The Lung as a Mirror of Systemic Disease

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This book is dedicated to the memory of my teachers

the late Dr Maurice Fishberg and

the late Dr Max Pinner

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E H R

Preface

IN THE FOLLOWING pages a number of diseases are described in which the lungs may mirror what is happening in other parts of the body. The sequence in which the various diseases are presented is primarily for orientation purposes. It is not intended to serve as a classification in the generally accepted sense of the term since it is often impossible to draw sharp distinctions between one group of diseases and another. Several of the conditions to be described cannot be fitted at present into any classification because they are too fluid to be pigeon holed into specific compartments. With the development of new techniques in diagnosis and treatment, diseases and syndromes are constantly being discovered, occasionally rediscovered, and new ones created. This involves an endless reclassification. As aptly stated by Bohrod, "There is no such thing as a correct classification, there are only useful classifications."

This volume is a segment of medicine with emphasis on disseminated diseases which may be associated with pulmonary lesions as part of the basic disturbance. This explains why considerable description is included of the disease as a whole as well as of the pulmonary lesions. In fact, it will appear at times that more space is allotted to the former than the relatively insignificant lesions in the lungs would seem to warrant.

In justification of certain liberties taken, it bears emphasis that the chest x-ray, the keystone of diagnosis of pulmonary diseases, is a window not a portrait and often mirrors passing events. One is also mindful of the fact that an apparent rarity, once recognized, often becomes commonplace. Certainly, for every patient with rare or bizarre pulmonary lesions, discovered in specialty practice, many times the number pass through the offices of general practitioners, and even hospital wards, with their disease either unrecognized or misdiagnosed. It is hoped that this book will alert the physician to the wealth of information obtainable in a chest x-ray provided the latter is viewed in broad perspective.

Thesis

Routine x rays of the chest of apparently healthy individuals are a consta
reminder that a silent chest does not necessarily contain healthy lung
and that a noisy chest need not connote serious disease The presence o
absence of disease can be established only by a chest x ray the finding
viewed in the light of the patient s history physical signs and pertinent labo
ratory tests Occasionally the chest x ray reveals abnormal markings of a
type and distribution which are suggestive of these being the manifestations
of a systemic disease In such the chest x ray may be the first to draw atten
tion to the presence of a widespread disturbance which might otherwise
escape detection Or else the information obtained may be of additional
help in differential diagnosis In either case the lung may serve as a mirror
of what is going on in organs and tissues of the body not accessible to direct
examination

Although roentgenography and its various modalities occupy a key posi
tion in chest diagnosis and will be featured in the following pages it would
be foolhardy to minimize the value of other means of investigation A history
obtained by the physician a thorough physical examination and the necessary
laboratory tests including bronchoscopy bronchography and when indi
cated lung biopsy are as essential in arriving at a diagnosis as are the roentgen
findings In fact there are occasions when the physical examination is more
informative than the chest x ray findings and the history superior to both
However in the diagnosis of obscure systemic disease with pulmonary lesions
of the type to be discussed in these pages physical signs are usually lacking
and one may have to resort to all available diagnostic measures and the true
nature of the disease may still remain elusive

Insofar as roentgen diagnosis *per se* is concerned there is nothing pathog
nomonic about lights and shadows in a chest x ray An area of density may
represent consolidation caused by neoplasm pneumonia tuberculosis or a
transient atelectasis caused by temporary obstruction of a bronchus A cir
cumscribed area of translucency may represent a cavity caused by abscess
tuberculosis neoplasm or lung cyst The abnormal roentgen markings assume
added significance when viewed on a background of what the physician
knows of the patient s family and past history occupation travels as well as
the physical and laboratory findings The black and white shadows then
assume various shadings With experience the presence of a particular
disease may be suspected or diagnosed with a high degree of accuracy on
the basis of the roentgen findings alone A definitive diagnosis *always* re
quires confirmatory evidence

Broadly speaking diseases affecting the lungs may be grouped into one of three categories (1) *Primary Diseases* These include developmental defects new growths traumatic injuries and similar conditions The majority of the acute bacterial and viral pneumonias pulmonary suppurations primary pulmonary neoplasms and tuberculosis typify this group (2) *Secondary Diseases* These include pulmonary emboli metastatic malignancies and so called terminal pneumonias (3) *Concomitant Diseases* In these the respiratory tract is involved either initially or in the course of systemic diseases as an active more or less co equal participant These pages are concerned primarily with the last mentioned

When the lungs are involved as part of a systemic disease the following are noteworthy (1) a symmetrical distribution of lesions in both organs (2) a vascular or perivascular pattern of abnormal lung markings and (3) a tendency toward pleural implication The first and second elements are related to the fact that the pulmonary involvement in most systemic diseases is either within or along blood vessels and/or lymphatics The third is due to the fact that the pleura is richly supplied with blood vessels and lymphatics

The pulmonary changes giving rise to abnormal roentgenologic patterns are a composite of (1) normal bronchovascular markings which vary with the age sex occupation and body build of the individual also the conditions under which the roentgen examination is made (2) physiologic and pathologic changes within the air containing units of the lungs which largely determine the radiotranslucency of the affected parts and (3) specific architectural alterations in the way of fibrosis emphysema consolidation or necrosis as well as associated reaction in pleura lymph nodes and adjacent structures In toto the various elements mentioned endow the lights and shadows in the chest x ray with certain qualitative and quantitative characteristics which immediately bring to mind certain possibilities to be considered in differential diagnosis

A disease may manifest itself in the lungs in diverse manner and dissimilar diseases in comparable manner The pulmonary changes may assume the configuration of prominent hilar densities accentuation of bronchovascular markings diffuse fibrosis small or large air cysts miliary or nodular infiltrations patchy or massive consolidations or multiple cavities with or without an accompanying pleural effusion More often there is a combination of the aforementioned Yet these several patterns may be the result of a single or a limited number of agents On the other hand diffuse interstitial fibrosis may be the end stage of viral pneumonia allergic pneumonia sarcoidosis scleroderma chronic pulmonary congestion and other diseases Cystic changes may be associated with pituitary disease histiocytosis tuberous sclerosis and other diverse conditions At least fifty abnormal states may give rise to miliary or nodular foci It would take us too far afield to enumerate the diseases which may give rise to pulmonary consolidation cavity formation or pleural effusion The totality of the picture depends on the type of tissue involved the duration of the disease and the intensity of the pathological process As the disease progresses or becomes chronic and recrudescent the causative agent plays an increasingly lesser role as far as determining the final picture

THESIS

There are times when one has the impression that the changes in the lungs as depicted in the chest x rays are in keeping with the presence of a systemic disease, yet one may be unable to demonstrate organ or tissue involvement outside of the chest. This state of affairs is exemplified in instances of diffuse interstitial fibrosis, cystic lung and other obscure conditions currently being met with increasing frequency. It may be speculated that in some the pulmonary changes represent the end stage of a disease at one time widespread; in others the lungs may be momentarily the shock organs of a systemic disease, the nature of which is obscure. We have learned by analogy that sarcoidosis was originally described as a dermal disorder; in time, it was recognized as a systemic disease and now is often found in the lungs and regional lymph nodes without demonstrable involvement of other organs. One of the purposes of this book is to indicate the possibilities of similar eventualities with respect to other diseases.

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Chapter 1

Chest Roentgenography in Mass Surveys

Introduction

CHEST X RAY surveys of apparently healthy individuals were initially introduced as a means of finding tuberculosis but it soon became apparent that nontuberculous chest diseases including neoplasms bronchiectasis pneumonias suppurations cardiac abnormalities developmental defects and the pulmonary manifestations of various systemic diseases may also be detected in this manner. Chest x ray surveys have been most *fruitful in the detection of tuberculosis in vulnerable segments of the population* such as American Indians and Negroes in industries associated with occupational dust hazards in colleges armed forces establishments diagnostic and prenatal clinics penal and mental institutions and more recently general hospitals.

The introduction of photofluorography by Manoel de Abreu in 1936 utilizing small films has made the mass x ray survey an invaluable tool for case finding. The results obtained in the examination of armed forces personnel during World War II were so gratifying that routine chest roentgenography was soon widely adopted by various public and private health agencies.

The incorporation of a phototimer (Morgan) and the development of a 70 mm apparatus hastened the use of photofluorography for mass surveys. The basic feature in the mechanism involves a built in photo cell which scans the screen fluoroscence created by radiation through the central lung field. The mechanism automatically times the exposure necessary to produce films of any desired density. This assures *uniformity* in chest radiographs a desiratum in comparing films of the same individual.

The photoroentgen unit is installed either as stationary equipment or as a mobile tractor trailer unit with a self contained power generator. According to one recent estimate approximately fifty million small films were taken from 1946 to 1950 inclusive in the course of chest x ray surveys conducted by various public health agencies in the United States. This number does not include the many standard sized films taken by physicians in their offices the countless numbers taken in clinics and hospitals and the many retake films when screening examinations reveal abnormal findings.

Mass Chest X Ray Surveys

TUBERCULOSIS CASE FINDING

The value of chest x ray screening of a community depends on the percentage of the population covered by the survey and the effectiveness of the follow up of those suspected of having disease. The minimum age of persons examined in general surveys is usually fifteen years. However children are included if there is a history of tuberculosis contact. A major weakness in mass x ray surveys is the fact that although the screening may include as high as 80 per cent of a community the 20 per cent omitted is apt to have a proportionally larger number of persons with abnormal chest findings. Those who have reason to suspect that all is not well with them are more likely to stay away. This feature of mass radiography is well illustrated in a study conducted by the Ohio University Student

Health Service In the participating or volunteer group, tuberculosis was found in 0 11 per cent, in the "straggler" group the incidence was 1 19 per cent, or approximately ten times higher Since it is a common practice to project the same prevalence rates of tuberculosis and other chest diseases found in an examined group to the unexamined group, the sources of error in this type of figuring are obvious It is also well known that elderly persons do not respond to appeals to submit to chest x-rays as do younger ones Possibly this is due to the fear of the former that should the chest x-ray reveal disease their jobs might be at stake

As mentioned, the results of mass x-ray surveys parallel the thoroughness of the follow-up of disease suspects An abnormality found in the chest which cannot be verified adds little to the value of the procedure On the whole, mass x-ray screening brings to light many suspects but comparatively few with disease of clinical significance Furthermore, in view of the decreasing incidence of tuberculosis, the cost of finding "positive" x-rays in mass surveys is increasing and the law of diminishing returns is coming into play Greater efforts will undoubtedly be made in the future to examine the more vulnerable segments of the population Increasing emphasis will be placed on the findings of tuberculin positive reactors in children The younger the child with a positive tuberculin test, the more likely is one apt to find a source of infection at home In the case of infants under two years of age the chances of finding a household source of infection is more than 90 per cent It may be mentioned at this point that lately tuberculosis is being discovered much more often in persons over fifty years of age than in younger age groups, especially in males The old "seed bags" will continue to be a source of contagion for some time to come

As an example of an ambitious undertaking in a community-wide chest x-ray survey, one may cite the Los Angeles X-Ray Project In a county of about three million inhabitants fifteen years of age or over, one half responded and were x rayed satisfactorily (Table 1) Unknown cases of ac-

TABLE 1

FINDINGS ON CONFIRMATORY ROENTGENOGRAMS IN LOS ANGELES CHEST X RAY SURVEY COMPRISING 1 867 201 PERSONS OF WHOM 64 745 WERE ASKED TO RETURN AND 54 648 COMPLIED

Essentially negative	14 344
Evidence of old healed disease	9 216
Tuberculosis	18 785
Other chest disease' including 3 500 neoplasm suspects	5 646
Cardiovascular disease	6 657
	54 648

From Guiss *Cancer*, *8* 219, 1955

tive tuberculosis were discovered in 1 08 per thousand The extent of involvement, in cases of active disease, was minimal in 30 per cent and either moderately or far advanced in 70 per cent Drolet, who reported these statistics, makes the pertinent comment that mass surveys do not necessarily find the majority of active cases in the early stages of the disease A similar city-wide survey was conducted in Minneapolis Of approximately 500,000 inhabitants, 301,513 of the adult population were examined in a period of sixteen weeks Of those examined, 6,375 were found to have significant lesions These were referred to private physicians and clinics for further study A preliminary report of the results was made available of the findings in 3,228 cases The final diagnoses included (1) 261 persons with active pulmonary tuberculosis, 1,859 persons with inactive or arrested tuberculosis, and (2) 1,108 persons with a variety of nontuberculous diseases (275, cardiac, 122, cancer and 711, "other" conditions)

Community-wide surveys have been conducted in other metropolitan areas, including Erie County and Niagara Falls, New York, Muskogee County, Georgia, Seattle and Tacoma, Washington, Boston and Worcester, Massachusetts, Washington, D C, and Denver, Colorado With the cooperation of the United States Public Health Service, 22 such chest x-ray surveys were completed by 1953 Community surveys on less ambitious scales have also been conducted in various parts of Europe Insofar as the detection of pulmonary diseases are concerned, and tuberculosis *in particular*, the results vary to some extent with the composition of the popula-

tion On the average, between 2 to 3 per cent, at most four, of those examined are found to have abnormal chest x-ray findings requiring additional investigation One per hundred (1 0 per cent) is found to have lesions suspicious of tuberculosis and on further study, this percentage is reduced to 0 1 per cent (one per thousand) with clinically significant diseases The changing scene in tuberculosis in recent years will undoubtedly be reflected in considerably reduced morbidity rates in the future

Physicians engaged in x ray surveys repeatedly draw attention to the fact that community chest screening surveys disclose, in addition to tuberculosis neoplasms and cardiovascular suspects, as well as large numbers with "miscellaneous" conditions Gould found sixty-six different categories of chest lesions revealed in mass x ray surveys Many would not have come to light or would have been discovered in advanced stage if not for roentgenography In view of the decreasing importance which mass surveys will be occupying in the future in the detection of tuberculosis, it may be worthwhile to discuss briefly the value of this technique in the discovery of pulmonary neoplasms and heart disease The large "miscellaneous" group of diseases has, as yet, attracted little attention because of the complexity of the problem involved in the follow up and final analysis of such cases A major objective of this book is to draw attention to the "miscellaneous" or "other chest disease" group, an untapped source of material for future study

Cancer Case Finding

Chest x ray surveys are instrumental in the discovery of many cases of benign and malignant intrathoracic neoplasms Guiss in a tabulated summary of ten surveys, found the incidence of possible tumors, detected in chest x rays, to be 0 8 per 1,000 persons examined The Los Angeles survey, previously mentioned, disclosed 3,500 chest tumor suspects In 329, in whom the presence of tumor was confirmed, the disease was found malignant in 246 and benign in eighty three An additional number had metastatic lesions (108), goiter (464) and benign tumors not treated (298) (Guiss, cited by Drolet)

In a chest x ray survey in Boston, 536,012 persons were examined Suspicious tumors were found in 398 In thirty-nine the presence of primary bronchiogenic carcinoma was proved, in thirteen the diagnosis was presumptive Metastatic pulmonary tumors were found in nineteen The largest number, 275, fell into a miscellaneous group comprising eighty-one cases of tuberculosis, forty two other infections, fifty-one mediastinal lesions, fourteen chest wall lesions, thirteen diaphragmatic lesions, ten vascular lesions, forty-seven "others" and seventeen "no disease" McNulty draws attention to the thirty-nine patients with proved primary carcinoma Twenty-one, or 55 per cent, were resected but only 5 or 13 per cent, were alive and apparently well three years after the date of the original survey film Guiss reported a "three year cure rate" of the resected cases in the Los Angeles survey, previously cited, of 35 8 per cent, a considerably higher figure than that generally obtained in non-survey groups This reflects the inclusion of many patients with early, asymptomatic disease

Guiss notes that of the 3,500 tumor suspects discovered in the Los Angeles survey, only 9 per cent of lung cancers was found in the age group under forty five years (Table 1) He estimates that were the survey restricted to males more than forty five years of age, the number of lung cancers would have increased four- to five-fold As an indication of the effectiveness of the surveys, in discovering bronchiogenic carcinoma, is shown by the fact that only twenty-seven of those surveyed who were to die of lung cancer that year were not discovered by the single microfilm, in contrast to the 213 picked up But inasmuch as 11 per cent were missed, chest x rays should be repeated twice a year for greater effectiveness

The question arises whether carcinomas found in the course of mass surveys are more "curable" than those encountered in private practice and whether such tumors can be discovered in sufficiently large numbers to warrant consideration of the mass chest survey as a practicable means of pulmonary cancer control Since, at present, re-

section is the best treatment available the earlier the disease is discovered and excised the better the prospects of survival Resection is the treatment of choice for every unexplained mass in the chest especially in persons of the cancer age providing there are no contraindications to surgery This obviously involves exploratory thoracotomy and resection of many relatively benign circumscribed masses But this is a small price to pay since disease occupying space in the chest is best removed under any condition unless there are definite contraindications Garland estimates that photofluorographic screening procedures applied to the general population have led to the detection of about ten cases of bronchiogenic carcinoma per 100 000 persons examined But if the procedures were restricted to males over forty five and conducted every six months the yield should reach about fifty cases for 100 000

In a survey of 156 724 people Gowen and Frank reported the discovery of 307 with findings suggestive of malignancy Follow up of these suspects led to the diagnosis of fourteen with proved carcinoma the majority well advanced The report by Churchill on bronchogenic carcinoma discovered in the San Diego survey is particularly instructive Of 239 000 persons examined carcinoma was correctely diagnosed in twenty of whom seventeen died In the following two years an additional twenty *four* in whom the disease was not detected in the survey died of bronchiogenic carcinoma The average time *from* the screening to the onset of symptoms in the undetected group was nine months The symptom free period corresponds closely with that found by Buchberg Lubliner and myself in a study of 443 patients with fatal carcinoma of the lung proved at autopsy The duration of life from the time of onset of *striking* symptoms was 14 2 months from the time of appearance of *objective* findings 9 1 months

In view of the fact that only a small percentage of patients can be cured after symptoms develop it is obvious that screening once a year is too long an interval in which to discover symptomless carcinoma *of the lung Persons of* advanced age need to be examined at least twice a year In the final analysis the diagnosis and treatment of carcinoma of the lung is largely the responsibility of *the general practitioner The physician must* be impressed with the importance of taking a chest x ray as part of every complete health examination In the case *of men past forty years of* age with unexplained symptoms referable to the chest failure to include a chest x ray is indefensible Even in presumably *clear cut cases of* transient atelectasis or resolving pneumonia or pneumonitis of whatever cause follow up x rays should be taken until there is complete resolution of the process Only in this manner will cancer of the lung be discovered in resectable stages Recent reports on resectional surgery for malignant neoplasms expressed in five year survivals indicate results approaching 20 per cent twice as good as those reported only a few years ago

Heart Disease Case Finding

The Boston survey previously mentioned revealed some interesting information relative to the finding of previously unknown cardiac disease Rutstein and co workers reported observations on the validity of mass chest x ray surveys in detecting heart disease Each film was subjected to two *independent readings one by read*ers utilizing usual chest x ray survey techniques where the primary interest is the finding of tu*berculosis and a second by a group of radiolo*gists working in pairs who were solely interested in finding abnormalities in the size and shape of the silhouette of the heart and great vessels All persons whose shadows were classified as abnormal by either or both groups of readers were then requested to return to a special clinic staffed by cardiologists for confirmatory studies

Considerable variations were found in the yield of abnormal films in the two studies due to differences in training *and experience of the* readers in the interpretation of x ray shadows of the heart and great vessels Those who read the *films only for heart* disease contributed almost three times as many abnormal films as did those who read the films for all chest abnormalities with primary emphasis on tuberculosis The total yield of verified heart disease was 1 62 per cent

A comparable study in which all the films were read once only by a survey team for all possible chest abnormalities including those of the heart and great vessels yielded 0 23 per cent with verified heart disease It would seem therefore that although the small film may be used as a heart disease case finding procedure the value of such screening depends in the final analysis on a careful examination of each cardiac suspect For this reason as will be discussed later routine chest x rays of patients admitted to general hospitals and clinics are much more fruitful

Miscellaneous Diseases Discovered in Chest X Ray Surveys

Mass surveys include large numbers of suspects with undiagnosed chest disease Later chapters will deal at greater length with some of the conditions found among this miscellaneous group and the methods by which a diagnosis may be established in some of the suspects

It might be pertinent at this point to emphasize a weakness in chest roentgenography as applied to chest x ray surveys which is not sufficiently appreciated by those engaged in mass undertakings Suspicious lesions discovered in routine roentgenography and which are later found to be due to errors in technique or interpretation or after additional studies are finally judged as being of no clinical significance may be a cause of much worry on the part of the person and family concerned The several days perhaps weeks it takes before a verdict is reached is a period of stress which few individuals can bear with equanimity It is therefore important that persons requiring additional studies be examined as expeditiously as possible Furthermore the ones being examined should be told that suspicious lesions which may be found on routine roentgenography will more often than not turn out to be of no clinical significance and that when they are invited for follow up examinations it need not necessarily signify that disease has been found

An additional drawback to mass chest x ray surveys is the false sense of security it may engender on the part of those examined as well as on the part of the physician when the report is made that no abnormalities were found A negative report means that no demonstrable abnormalities were discovered *at the time of the particular examination* It does not guarantee that the lungs will remain immune to disease in the future

Multiple or Multiphasic Screening

In recent years attempts have been made to incorporate chest x rays taken during routine health examinations in multiple (multiphasic) screening programs The specific purposes for such undertakings are case finding as well as health education The method involves the use of two or more simple laboratory tests or procedures applied on a mass basis to determine presumptive evidence of incipient disease or defect This definition of the nature of multiple screening agreed upon at the National Conference of Chronic Diseases in 1951 does not imply that the particular examinations are in the nature of a diagnostic study no more than is the simple chest x ray of a pulmonary disease The procedures included in elaborate multiple screening programs are in addition to a chest x ray a serologic test for syphilis a hemoglobin determination an erythrocyte sedimentation test blood sugar and urine tests an electrocardiogram tests for sight and hearing defects height and weight measurements Papanicolaou smear examination for tumor cells and other refinements depending on the medical laboratory and administrative facilities available The most commonly used tests are chest x rays serologic tests for syphilis and blood sugar determinations The more ambitious projects even include a self screening history

In a review of multiple screening published by the Council on Medical Service of the American Medical Association (November 14 1953) the advantages as well as the objectionable features are discussed Among the many objections the following have been voiced A medical production line type of examination by machine cannot exclude or detect all incipient diseases also that it may engender a false sense of security in those in whom abnormalities are not found also that it may cause undue apprehension and

expense for those who are found to have false positive results" It has also been claimed that "the physician has no opportunity to secure an intimate knowledge of the patient" and that there is "no opportunity for an appraisal of the negative group by a physician" Probably the most important defect lies in the fact that "most of the tests that are employed do not possess even an approximately precise value or measure that, on the one hand may indicate that a finding is within physiological limits or, on the other hand, is really indicative of a disease process"

Among the major advantages of a multiple screening program, it is pointed out, are that it offers "an excellent preliminary procedure to any form of examination by reducing the cost and time factors thereby making it possible to extend periodic examinations to significantly larger groups of the population" It is claimed, furthermore, that "multiple screening program is an aid to making people health conscious and seems to stimulate the desire for regular check ups," and that "as a program of prevention, multiple screening has caused a large number of apparently well persons who were not aware that they might have a progressive disease to consult their physicians"

In summarizing the results of nine major projects, *totalling more than a million persons* screened, Kurlander and Carroll estimated that *approximately 50,000 or 5 per cent of the number* were found to have disease and/or major abnormalities previously unrecognized In several of the projects, the yield was as high as 10 per cent These investigators emphasize the fundamental differences between screening and diagnosis The former attempts only to select high prevalence groups through the application of standardized tests to numbers of people with the full realization that there will be errors in the form of false positives and false negatives Diagnosis, on the other hand, establishes or rules out disease through a synthesis of the most complete and accurate information available about a particular individual While each of these processes is appropriate in its place, they cannot be used interchangeably

Chest X-Ray Surveys of Selected Population Groups

Armed Service Personnel

World War II provided illuminating data on the lung findings of approximately 18,000,000 presumably healthy persons In an analysis of a sample of about 200,000 registrants, Morse found that 1 per cent had disqualifying chest disease of which 0 3 per cent had active pulmonary tuberculosis The relatively small number found with nontuberculous disease and the comparatively large number with tuberculosis was undoubtedly due to the age group of the registrants By the same token, the lungs of these individuals had not as yet sustained the wear and tear of life which explains the small percentage found with nontuberculous pulmonary disease The nontuberculous rejections, based chiefly on the roentgen findings, comprised thirty-five different categories

Medical Students and Nurses

Tuberculosis developing in the course of training of medical students and nurses is a serious problem The lowered incidence of this catastrophe in this group in recent years is due partly to the decline of tuberculosis in the general population *and partly to the institution of precautionary measures including* (1) *tuberculin testing* and chest roentgenography of all matriculants and at intervals during the course of training, (2) increased use of chest x rays in hospital and clinics enabling the discovery and segregation of those found tuberculous, (3) the adoption of contagious technique, (4) a more judicious use of tuberculosis clinical and autopsy material in teaching and (5) the establishment of student health departments in universities and colleges BCG vaccination in tuberculin negative reactors and the employment of city bred elderly nurses in tuberculosis institutions, a necessity in most cases because of the shortage of recent graduates, have helped materially in lessening the incidence of tuberculosis among the most exposed group of the population

Pre-employment Groups

Chest roentgenography is being used with increasing frequency in pre-employment examinations. Many states are adopting legislation liberalizing Workmen's Compensation Laws respecting tuberculosis, silicosis and other occupational hazards. This makes it all the more important for employers to discover chest disease in prospective employees which might become compensable. In many cities those employed as food handlers, beauticians and in department stores are required to have periodic x-rays of the chest. Teachers and school employees are receiving special attention in this respect. The results of routine chest x-rays of workers in low paid industries as well as indigents and recipients of public relief serve to emphasize the important role which the socioeconomic factor plays in tuberculosis.

Vulnerable Ethnic Groups

A major health problem in the United States is the high incidence of tuberculosis in several ethnic groups of the population, notably Negroes, Puerto Ricans and American Indians. Pinner and others believe that a true racial genotypic difference exists among various racial segments. The course of the disease and its response to treatment among white and non-white groups support this assumption. Undoubtedly contributing factors are present in the unfavorable economic status and living conditions of these people. Although the prevalence of tuberculosis, as indicated by tuberculin testing and recent x-ray surveys, is showing a steady decline, the morbidity and mortality rates among the segments of the population mentioned remain considerably higher than in the general population.

Inmates of Mental Institutions

Approximately 600,000 persons in the United States are in institutions receiving care for mental illnesses, approximately one half of all the patients hospitalized in the country. Chest x-ray surveys of inmates of mental institutions reveal a high incidence of tuberculosis. In fact, the rate is higher in this group than in the most vulnerable groups of the population at large. Because of the uncooperativeness of mental patients, difficulties are encountered in the diagnosis and treatment of disease so that repeated chest x-ray examinations are necessary. Among patients with dementia praecox the prevalence of tuberculosis is particularly high, probably because such patients stay longer in institutions and have therefore greater opportunities of developing the disease.

Oechsli reported the results of chest x-ray examinations of 25,914 mental patients in seven California hospitals. The study revealed 8.75 per cent of previously unsuspected reinfection type pulmonary tuberculosis and a tuberculosis death rate of over 600 per 100,000. Other investigators have reported similar high morbidity and mortality rates. The true prevalence of tuberculosis in mental institutions is not known because of various laws and regulations which hinder effective case finding programs. Equally important is the fact that a high incidence of tuberculosis is found among employees of mental hospitals and, to a lesser extent, among employees of institutions for mental defectives. Tuberculosis in mental institutions is a serious problem and comparatively little has been done toward its solution. Proper management involves a chest x-ray of every inmate on admission and periodic surveys of all inmates because one has to depend almost entirely on the x-ray in the detection of the disease. Effective treatment of pulmonary tuberculosis in patients of mental institutions involves intensive use of antimicrobial medication and resection of localized disease. Halfway measures are not enough.

Routine Chest X-Rays in General Hospitals

The routine use of roentgenography for the detection of chest diseases in patients entering general hospitals has not received the wide adoption the procedure merits. All too often chest x-rays are taken of such patients days or weeks after admission or *when indicated*, a contingency which may or may not arise and when it does, after loss of valuable time. The fact is not sufficiently stressed that a hospitalized pa-

tient with undiagnosed active pulmonary tuberculosis is a source of danger to others including physicians nurses and other hospital personnel On the other hand a patient with a nontuberculous chest disease may be under treatment for a relatively minor ailment while the more serious illness remains undiagnosed The patient may leave the hospital with disease undetected which might have been treated effectively

In 1934 Hodges made a test of the utility of routine chest x rays of all patients during fourteen consecutive working days The examinations were of patients entering the clinic as well as the hospital After the films had been processed they were put away At the end of three months they were re examined and compared with the hospital records to see whether or not the examinations might have been helpful in diagnosis It was found that a gross error of omission had been made once every day during the fourteen day period Realizing that one could not afford to make an error of that extent routine photofluorography was introduced in the hospital beginning in 1941 Over a span of seven years a total of 176 304 admission survey examinations were made including 6 285 examinations of hospital employees Of the total number examined 9 4 per cent were considered on the initial review to be sufficiently abnormal to require further study The figure of 9 4 per cent remained constant month by month throughout the seven years On the basis of periodic samplings it was found that the percentage of clinically important chest abnormalities among the survey groups shrank from 9 4 per cent to 5 7 per cent when the initial abnormality was more carefully evaluated by other means of investigation

Oatway in a survey of the status of routine chest x raying in 539 general hospitals in the United States as of September 1948 found that 247 hospitals or 6 6 per cent had routine chest x rays taken of patients on admission and of these comparatively few included all the admissions It should be mentioned that the directory of the American Medical Association lists approximately 4 600 general hospitals and a minority of these provide routine chest x ray of hospital admissions

As recently as 1950 Porter in a survey of the hospitals of New York City found only ten of 138 institutions to have a program of x raying patients on admission These ten institutions accounted for 6 5 per cent of all the patients admitted to the 138 hospitals approximately the same percentage as that found by Oatway Since it is estimated that 30 000 000 persons are treated yearly in the general hospitals of the United States it is obvious that these institutions harbor large numbers of individuals with undetected chest disease Since the discovery of the pulmonary manifestations of systemic disease the topic of our discussion is directly related to the problem of routine chest roentgenography of hospital admissions it may be pertinent to cite our experience at the Morrisania City Hospital This project initiated in 1948 was the first of its kind established in the Department of Hospitals of the City of New York

The case finding project at the Morrisania City Hospital was instituted with the following objectives (1) to determine the prevalence of pulmonary tuberculosis in patients admitted who were unaware of their disease (2) to protect physicians nurses patients and other hospital personnel from contact with unknown cases of tuberculosis (3) to discover the presence of nontuberculous chest diseases (4) to provide a teaching medium for physicians house staff and medical students (5) to determine the value of routine miniature roentgenographic examination of the chest as an auxiliary to standard equipment and (6) to help establish procedures which might serve as a pattern for other hospitals

Through the generosity of the Bronx Tuberculosis and Health Committee a 70 mm photofluorographic unit was installed in quarters adjacent to the admitting room of the hospital Miniature x ray films are taken routinely of all patients admitted to the wards excepting those in critical condition If an x ray is not taken on admission every effort is made to take one while the patient is in the hospital or upon leaving the institution Patients attending the prenatal clinic

TABLE 2

S. R. 1556-I (4-52)– 0M sets 506025(53)

Date

THE CITY OF NEW YORK
DEPARTMENT OF HOSPITALS

MORRISANIA CITY Hospital

ADMISSION X-RAY REPORT

☐ In Patient (Service)

☐ Out Patient
☐ Prenatal ☐ Multiphasic
☐ Diagnostic ☐ Other

☐ Employee (Division)

Last Name First Middle

Ward History or OPD # Date Adm Admission Diagnosis

Age Sex M ☐ F ☐ Color W ☐ N ☐ Other—Specify ☐ Marital Status S ☐ M ☐ W ☐ D ☐ LS ☐

Nativity Occupation

Film Nos Technician

FINDINGS

Tuberculous

TYPE OR DEGREE

1 ☐ Primary Infection
2 ☐ Minimal
3 ☐ Mod Adv
4 ☐ Far Adv
5 ☐ Pleural Effusion
6 ☐ Hematogenous
7 ☐ Silicotuberculosis

CLINICAL STATUS

1 ☐ Inactive
2 ☐ Active
3 ☐ Undetermined Activity

Non-Tuberculous

1 ☐ Pulmonary Disease (Tentative Diagnosis)
2 ☐ Pleural Disease
3 ☐ Abnormal Aorta
4 ☐ Abnormal Heart
5 ☐ Mediastinal Disease
6 ☐ Lung Anomaly
7 ☐ Rib Anomaly
8 ☐ Thoracic Cage Lesion
9 ☐ Lung Scars
10 ☐ Pleural Scars
11 ☐ Diaphragmatic Disease
12 ☐ Chest or Lung Injuries
13 ☐ Neoplasm
14 ☐ Others — Specify

CONCLUSIONS

1 ☐ NEGATIVE CHEST
2 ☐ ABNORMAL CHEST No further X ray unless clinically indicated
3 ☐ ABNORMAL CHEST Further study recommended

FINAL DIAGNOSIS

M D

have chest x-rays at the time of registration so that when they enter labor they are taken immediately to delivery rooms. On an average, about 85 per cent of the patients admitted to the hospital are examined by miniature roentgenography, the remaining 15 per cent being composed largely of emergency admissions. Chest x-rays are taken on a twenty-four hour schedule. The films are developed at the end of each day, excepting week ends and holidays, and read the following morning.

The resident in pulmonary diseases begins the day's work by reading the films taken the previous day. A staff physician of the Pulmonary Division checks the resident's findings and reads, in addition, all films taken since his last reading. In the course of the week each film is read independently by at least two members of the visiting staff expert in roentgen interpretation of chest disease. An orientation sheet containing a concise notation of the roentgen findings is sent to the ward within twenty-four hours of the patient's admission. The upper half of the orientation sheet is filled out on admission, the lower half, after the final diagnosis is made. The sample of data to be presented shortly is based *on the final diagnosis* (Table 2).

Patients suspected of having pulmonary tuberculosis on the basis of the admission x-ray findings are immediately transferred to the tuberculosis wards. The condition of patients revealing nontuberculous diseases is brought to the attention of the physicians of the particular service involved, the members of the Pulmonary Division maintaining close contact with the patient and supervising the treatment until the final disposition. Follow-up is continued in the Chest Clinic. The direction and operation of the admission chest x-ray program at the Morrisania City Hospital is by physicians specializing in chest diseases. Institutions without a chest unit utilize a "Tuberculosis Officer" or some similar agents to integrate the several services.

As noted in the orientation sheet, three broad groupings are used in classifying the admission chest x-ray findings (Table 2). Group A includes instances in which no changes are seen in the miniature films of sufficient importance to warrant reexamination by 14 x 17 mm films. This group includes malformations or developmental anomalies of the thoracic cage or of the lungs such as azygos lobes or cervical ribs, discrete calcified foci, pleural thickenings or obliteration of costophrenic sinuses as well as diffuse emphysematous changes or accentuated bronchovascular markings in older age groups. In questionable cases the film is over-read, proper consideration being given to the admission diagnosis.

Group B includes instances of cardiac enlargement and/or undue prominence of the large blood vessels. Patients with such abnormalities are referred to the Cardiovascular Division. If the cardiac enlargement is associated with gross disease in the lungs and/or pleura such as infarction, pneumonia or large pleural effusion, the condition is classified in Group C. The latter includes all patients whose films show changes in the lungs and/or pleura of sufficient significance to warrant further study by 14 x 17 mm films and other diagnostic aids, if necessary. Since the installation of the photofluorographic unit at the Morrisania City Hospital approximately 1,200 "chest cases," exclusive of 800 cardiac suspects, are found annually.

Of the first 20,000 consecutive admissions to the Morrisania City Hospital 2,644 or approximately 13 per cent revealed significant chest ab*normalities (Table 3). An additional 8 per cent,* not included in Table 3, revealed cardiovascular abnormalities. In other words, one of every five patients admitted to the Morrisania City Hos-

TABLE 3

CHEST ABNORMALITIES AMONG 20,000 CONSECUTIVE HOSPITAL ADMISSIONS DISCOVERED ON ROUTINE PHOTOFLUOROGRAPHY

Service	*Tbc Known on Admission*		*Tbc Unknown on Admission*		*Non-Tuberculous Pulmonary Disease*	
Medicine (including *Chest Division*)	369		244		1428	
Surgery	16		39		140	
Urology	10		27		69	
Obstetrics and Gynecology	9		29		29	
Prenatal	11		19		18	
Other Services	15		58		114	
	430	2.15%	416	2.08%	1,798	8.99%

pital has abnormal findings referable to the heart and/or lungs to which attention is drawn often for the first time, through the use of routine chest photoroentgenography A follow-up study of the cardiac suspects was not made but there is reason to believe that in a sizable percentage the admission chest x ray was instrumental in directing attention to the possible existence of cardiac disease

The experiences reported by Butt and co workers are worth citing During 1953, photo fluorograms of all adult patients admitted to the Hospital of St Raphael, New Haven Conn were studied for cardiovascular disease In addition to the routine P A film, a left lateral view was taken on all patients except the very obese and the prenatal group Suspicious cardiovascular silhouettes were selected for further study Of 6,439 adults 709 of whom were suspected of having cardiovascular abnormality, a follow up study of 595 revealed 497 (83 per cent) to have cardiovascular disease One hundred and ninety-six (47 per cent) were unaware of the presence of such diseases Admittedly the patients were of a selected group and of more advanced age than are encountered in usual surveys Nevertheless the results are quite impressive

Study of a group of 601 consecutive patients with tuberculosis during the first two years of the Morrisania City Hospital project showed that 288 or 28 per cent knew of their disease on admission the majority having been referred for emergency treatment and 313 or 52 per cent were unaware of their disease On the basis of the total admissions to the Morrisania City Hospital, examined by routine chest roentgenography 2 08 per cent of the patients were found to have pulmonary tuberculosis for the first time, an incidence of more than 20 per thousand It should be noted that in contrast to the group admitted with known tuberculosis, those with unknown disease included only 15 per cent with advanced and 60 per cent with minimal tuberculosis

The clinical material at the Morrisania City Hospital comprises a select group of patients including large numbers of Negroes and Puerto Ricans in whom tuberculosis is much more prevalent and more virulent than in the general population The recent decline in the incidence of tuberculosis in the population as a whole is probably being neutralized to some degree by the fact that in large urban centers, as in New York City, non-whites are now making up a larger percentage of the population Obviously, a case finding study in a hospital located in a section of the city with a smaller percentage of Negroes and Puerto Ricans than in the Morrisania district would undoubtedly reveal a lesser incidence of tuberculosis In any event, the incidence would be materially higher in routine hospital admissions than in the general population The finding of more than twenty persons per thousand with clinically significant tuberculosis among routine admissions to the Morrisania City Hospital who were unaware of their disease is impressive As mentioned previously, community surveys reveal an incidence of reportable or "probably" active tuberculosis of one to three per thousand

From the very inception of the project at the Morrisania City Hospital particular attention was paid to the problem of pulmonary neoplasms It was found that although a sizable number of unsuspected tumors are discovered in the course of routine chest photofluorography, the vast majority are in advanced stages and not amenable to surgical treatment One of the reasons few cases of early carcinoma of the lung are discovered among general hospital admissions is because the majority of patients enter the institution with acute disease or acute episodes superimposed on chronic illnesses In a patient with bronchiogenic carcinoma associated with symptoms, the disease is almost invariably too advanced to be benefited by surgery However, one should not lose sight of the fact that benign intrathoracic neoplasms are also of serious import because of their location within the restricted confines of the chest cavity Since surgery offers the most rewarding results in the treatment of benign intrathoracic neoplasms the discovery and removal of such tumors, as a result of routine chest photofluorography, are notable achievements in themselves

In addition to its practical value as a case finding method, a photofluorographic machine in-

stalled in a hospital serves as an auxiliary to the department of roentgenology The unit may be used for the examination of those seeking employment as well as in the routine examination of house physicians nurses and other hospital personnel The admission film is occasionally the sole means of demonstrating chest disease because once a patient is in the ward the rapid deterioration of his condition may prevent more thorough roentgenologic studies The establishment of a photofluorographic unit in an institution makes physicians chest conscious by providing almost daily examples of what might have been missed had a chest x ray been omitted

A chest x ray should be included as part of the preoperative preparation of every patient about to undergo surgery Since patients are often operated on shortly after hospitalization this procedure is often omitted with catastrophic results in some cases Patients with chronic pulmonary diseases such as pulmonary tuberculosis bronchiectasis and neoplasms who are scheduled for operation on a later date should have chest x rays taken the day prior to operation to note any last minute developments Occasionally one meets with unexpected changes in the chest x ray which may prompt postponement of the contemplated operation

A request card for a chest x ray can be made part of the preop orders The chest x ray is read the same day and any abnormal findings immediately relayed to the *anesthetist and surgeon* Loder reported on the use of this technique in 1 000 consecutive surgical cases In 116 cases *abnormalities* were found and in twenty nine *of these* operations were postponed or cancelled This number included six newly discovered cases of pulmonary tuberculosis three cases of carcinoma two cases of severe pulmonary collapse and infection and a variety of other conditions Significantly in three cases early in the series reports of the roentgen findings were received too late and operations were done These patients developed postoperative complications

Routine Chest X Rays in Clinics

Increasing numbers of patients are having chest x rays in out patient departments of general hospitals and in special clinics connected with various institutions Unfortunately the number of clinics utilizing this valuable diagnostic aid as a routine measure is still small Yet in some respects the early diagnosis of chest disease in clinic *patients is even more pressing than* in patients occupying hospital beds Expeditious handling and segregation of patients in city hospital clinics is urgent The examining rooms and corridors are apt to be filled with patients having minor ailments as well as those with major diseases including acute infections requiring immediate admission to the wards Too much time is lost in most clinics before a chest x ray is taken which in a properly organized unit should be made of each patient on registration The chest x ray should not be reserved for problem cases , one meets with more problem cases after chest x rays are taken

The results of routine roentgenography of all prenatal registrants at the Morrisania City Hospital have demonstrated the value of this procedure Of 2 400 consecutive prenatal registrants in a period of two years no *less than* 40 (1 7 per cent) were found to have clinically significant pulmonary tuberculosis some with advanced disease In twenty two the disease was discovered for the first time by the routine employment of photofluorography An additional thirty one were found to have various nontuberculous conditions exclusive of cardiac diseases requiring further study Interestingly enough a study made some years ago in the prenatal clinic of the same institution revealed one defect to every four patients but *not a single instance of pulmonary tuberculosis* Needless to say routine roentgenography was not used at the time this particular study was *made*

The experience at the Morrisania City Hospital with prenatal registrants *has been* duplicated in other institutions *Bickerstaff and co* workers found on routine photofluorographic examinations of 3 576 prenatal cases 43 or 1 2 per cent with tuberculosis or suspected tuberculosis 25 or 0 7 per cent with cardiovascular *disease and a number* with other conditions The unusually large percentage of Negroes and

Puerto Ricans among the Morrisania City Hospital prenatal registrants accounts for the high incidence of tuberculosis found in this hospital group Bickerstaff and his co workers draw attention to the important finding that a comparison of the group of patients whose tuberculosis was diagnosed prenatally with those whose disease was discovered for the first time postpartum showed a much more disastrous course of events in both mothers and infants in the latter group

Convincing proof, if any additional evidence were needed, of the importance of routine chest roentgenography in the diagnosis of pleuropulmonary disease is available in chest clinics where patients are referred by physicians with the knowledge or strong suspicion that pulmonary disease is present In 1950, N Wynn Williams had roentgen examinations made of 228 consecutive patients diagnosed as having 'pneumonia' These were routine referrals by physicians to his chest clinic Twenty seven patients suspected of having pneumonia but in whom the x rays failed to reveal evidence of disease were excluded from the study Those with abnormal chest x rays were followed until a 'normal" film was obtained or a definitive diagnosis established In 156 the diagnosis of pneumonia was confirmed the disease resolving in the course of time In nineteen a second pulmonary condition not related to the pneumonia, was discovered as a result of the roentgen examination In forty, or about 20 per cent, the diagnosis was incorrect Instead of pneumonia, the disease proved to be tuberculosis pleural effusion, bronchiectasis, neoplasm, cardiac disease or some other cause In brief, 'pneumonia," a disease easily recognized by the average physician, when subjected to the light of roentgenography may turn out to be anything but pneumonia

As indicated in the preceding pages, unsuspected chest disease is discovered occasionally in apparently healthy persons and much more often among hospital patients It stands to reason, therefore, that those seeking attention in physicians' offices probably occupy an intermediary position insofar as the incidence of discoverable chest disease is concerned This presumption is borne out by the experience of physicians in chest clinics where patients suspected of having disease are referred by their private physicians Southerland established a radiographic center for patients of general practitioners Of all the physicians in the community, 280 or approximately 50 per cent availed themselves of the service The patients were first screened by miniature films and, when necessary, large films were used Those found to have significant abnormalities were referred to more specialized thoracic units Of a total of 5,072 persons examined, 227 or approximately 4 per cent were found in need of more intensive investigation The final diagnosis of the 227 included 154 with active pulmonary tuberculosis of whom 125 had acid fast bacilli in the sputum Twenty had intrathoracic new growths and the remainder, a variety of non tuberculous diseases

The importance of Southerland's study lies in the fact that a center of this type bridges the gap between the general practitioner, who may not have adequate radiographic equipment readily available, and the thoracic unit in a regional hospital where problem cases can be studied more intensively by a team of physicians and surgeons expert in their respective fields The radiographic center serves the additional purpose of enabling general practitioners to refer patients to a unit which is not designated specifically a tuberculosis clinic Many patients fear the publicity associated with a visit to a tuberculosis clinic and the inevitable visit of a public health nurse should a 'spot" be found in a lung In a radiographic center, such as the one conducted by Southerland, a preliminary screening is immediately available If an individual is found to have a suspicious lesion, it is usually not difficult to pursue the matter further

Routine Chest X Rays and the Private Practitioner

It is estimated that approximately 16 to 18 million persons in this country consult physicians annually The office of the private practitioner is obviously an ideal place for finding chest diseases providing full use is made of the opportunities and adequate facilities are made available for

diagnosis Unfortunately, promotional activities, incident to short term intensive case finding projects have concentrated their appeal to the selling of "free x-rays" to the masses Comparatively little attention is directed to the unique position which the practitioner occupies in his relation to the sick person The wealth of case finding material available in a general practitioner's office was strikingly demonstrated by one physician, Dr A C Daniels, in his own practice in Marion County, California

Dr Daniels' report covered a short period from October, 1941 to April, 1942 During this time he fluoroscoped routinely 250 persons which included all new patients who passed through his office In suspected disease 14 x 17 in films were taken This procedure resulted in the discovery of seven cases of active pulmonary tuberculosis, an incidence of 2 8 per cent Only one patient had physical signs suggestive of the disease and another suspected that he might have tuberculosis Comparing these results with his previous experience, Daniels noted that he had discovered five cases of active tuberculosis in the preceding seven years On the basis of his findings, this investigator estimated that if the prevalence of 2 8 per cent of active cases discovered in his practice were applicable to that of other physicians in the same community, the 15,000 patients who consulted doctors would have revealed about 400 cases of active tuberculosis The doctor's office represents a "great natural sieve" operating day in and day out through which are channelled patients not only with tuberculosis but other chest diseases, many with abnormalities of a type to be discussed in the chapters to follow

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Chapter 2

Diseases of Metabolism

Introduction

THE METABOLIC diseases which may affect the lungs are usually encountered in infancy and early childhood Those appearing later in life may occasionally be traced to an earlier age but in many instances this is not possible because developmental adjustments during growth tend to obscure the underlying defect Recurrent respiratory infections are also apt to becloud the nature of the original disease However, there is reason to suspect that certain cases of cystic lungs diffuse interstitial pulmonary fibrosis atypical forms of bronchiectasis and several other conditions to be described later, discovered for the first time in adults, represent late manifestations of disease either developmental in origin or which appeared shortly after birth

The reason why comparatively few metabolic disorders with pulmonary involvement are encountered in adulthood is due to the fact that children with major metabolic derangements seldom reach maturity With greater awareness of the nature of some of the metabolic diseases and the widespread use of antibacterial agents to combat infection, more children are now reaching adulthood This is attested by the increasing number of cases currently being reported of metabolic diseases with pulmonary involvement in older age groups

Metabolic diseases may affect the lungs through structural damage of the organs and by providing conditions favoring infection The latter is an almost inevitable accompaniment of several of the disturbances to be discussed In view of the profound alterations which take place in the vascular and internal secretory organs, as well as in the reticuloendothelial system, it may be pertinent to dilate on certain aspects of the problem which have an important, although indirect, bearing on the major topic of the discussion

Hypertrophic Pulmonary Osteoarthropathy

As described originally by Bamberger, and amplified by Marie, hypertrophic pulmonary osteoarthropathy is a symmetrical osteitis of the four limbs chiefly localized to the phalangeal and terminal epiphyses of the long bones of the forearm and leg, sometimes extending to the roots of the limb and flat bones and accompanied by a dorsal kyphosis and some affection of the joints ' The original description of the condition is therefore, more inclusive than simple clubbing of fingers and toes According to Hansen, clubbing and osteoarthropathy are similar reactions They may be independent of each other or one may precede the other Finger clubbing is more apt to occur in association with bronchiectasis and diffuse pulmonary disease, the condition developing and disappearing rather slowly Periosteal proliferation is more likely to be associated with carcinoma and localized pulmonary disease, the condition developing and disappearing more rapidly

As far back as antiquity, physicians have speculated on the possible relationship between digital clubbing and various diseases At first, clubbing was noted in association with chronic diseases, notably pulmonary tuberculosis, bronchiectasis lung abscess, empyema and congenital heart disease Later a considerable number of other conditions were found to be accompanied with finger clubbing A congenital form, with-

out changes in long bones is also recognized. A partial list of diseases in addition to those mentioned which may be associated with hypertrophic pulmonary osteoarthropathy includes carcinoma of the nasopharynx and thymus, malignant lung and pleural tumors, myelogenous leukemia, chronic valvular heart disease, cirrhosis of the liver, ulcerative colitis, chronic pyloric obstruction, sprue, pulmonary and peripheral arteriovenous aneurysms. Wierman and coworkers analyzed the occurrence of articular manifestations in 1,0?4 cases in which resection was done for major pulmonary diseases. As shown in Table 4, the highest incidence is reported in pleural mesotheliomas, lung abscess and cysts. Harper and Patterson draw attention to the fact that occasionally pulmonary osteoarthropathy may precede classic symptoms and signs of carcinoma of the lung. They found reports of forty-seven cases in which the interval ranged from two to thirty-six months.

TABLE 4

RELATIVE INCIDENCE OF PULMONARY OSTEOARTHROPATHY AS SEEN IN PLEUROPULMONARY RESECTIONS

Specific Lesions	*Resections*	*Arthropathy Present*	*Incidence %*
Pleural mesothelioma	14	8	57.1
Bronchiectasis	189	18	9.5
Lung Abscess	34	6	17.6
Cyst	30	3	10.0
Malignant tumor	481	5	5
Tuberculosis	157	1	0.6
Miscellaneous benign tumors, granulomas, etc.	119	0	0
Total	1 0 4	61	6.0

From Wierman, Clagett and McDonald: *J.A.M.A.*, *155*: 1460, 1954.

Various explanations have been offered for the development of hypertrophic pulmonary osteoarthropathy. These include anoxic, infectious, neuritic, toxic and endocrine factors. There is indirect evidence that in some cases the condition is related to an endocrine imbalance. This hypothesis finds support in a number of reported instances of osteoarthropathy occurring in patients with thyroid disease, a condition in which the pituitary gland plays a vital role. Thomas and others reported cases of osteoarthropathy occurring after subtotal thyroidectomy for exophthalmic goiter. Signs of osteoarthropathy appeared coincidentally with symptoms of postoperative hypothyroidism. After the institution of thyroid treatment there was noted a thinning of the subperiosteal bone as well as clinical improvement.

In 1915 Locke drew attention to the fact that acromegaly is so closely related to hypertrophic pulmonary osteoarthropathy that in some of the cases reported in the literature patients with acromegaly had been included among those considered to have pulmonary osteoarthropathy. In one instance of primary carcinoma of the lung the patient was found to have hyperplasia of the pituitary chromophil cells. Fried reported four cases of bronchiogenic carcinoma associated with advanced degrees of pulmonary osteoarthropathy. In his cases also the presence of acromegaly was attested by characteristic facies, tufting of the terminal phalanges of the fingers and toes, hirsutism, macroglossia and thickening of the cranial vault. Fried concluded that diffuse osteoarthropathy found in neoplastic diseases of the lungs is due to an endocrine imbalance akin to acromegaly.

Ray and Fisher noted that osteoarthropathy is much more often associated with peripherally situated malignant neoplasms than with main bronchial tumors. In rapidly developing osteoarthropathy associated with bronchiogenic carcinoma there may occur a painful arthritis, at times also peripheral neuritis. Ellman encountered six cases in a group of 200 consecutive bronchial carcinomas who presented joint manifestations in the form of acute or chronic polyarthritis as the initial complaint. In none was there any real evidence of extensive tissue breakdown or appreciable infection to account for the joint symptoms. Semple and McCluskie studied twenty-four patients who had joint symptoms in association with lung cancer. They showed clinical and roentgenological evidence of hypertrophic pulmonary osteoarthropathy. In thirteen patients who survived tumor resection they noted increased joint mobility often within hours of the operation. Patients who had been

bedridden with 'arthritis' for weeks or months were walking normally within a few days

The mechanisms involved in the development of osteoarthropathy are not clearly understood They are certainly too complex to be resolved by a single formula The presence of symptoms *of rheumatoid arthritis especially if the latter is* associated with acromegalic features and finger-clubbing, should direct attention to the possible presence of a bronchiogenic carcinoma Chest x rays should be taken in various projections to make certain that a small neoplasm is not lurking behind the heart or is hidden in some other recess of the thoracic cage (Figure 1) Ellman suspects that the reason for the dramatic response of the joint swellings to lung resection for carcinoma *might be in factors intrinsic in the lung itself* Vogl and co workers suspect that an abnormally increased peripheral blood flow plays a role in the pathogenesis of pulmonary osteoarthropathy The derangement of the circulation may be dependent upon an abnormal intrathoracic reflex which is promptly abolished by surgical removal of the affected lobe Flavell obtained marked symptomatic improvement of the osteoarthropathy, in irremovable bronchial carcinoma, by severing the vagus nerve alone on the affected side *This points to a neural reflex as one of the* mechanisms involved

Bloom documented a case in which metastatic lesions from a primary carcinoma of the lung were found in the pituitary gland There was hypertrophic pulmonary osteoarthropathy associated with acromegalic features A report by Peabody draws attention to the occasional association of bronchiogenic carcinoma and diabetes insipidus In six cases the evidence strongly fa*vored the assumption that the latter was a mani*festation of metastases involving the posterior lobe of the pituitary gland In an additional six cases, culled from the literature, the diabetes insipidus was found to be caused by metastases in

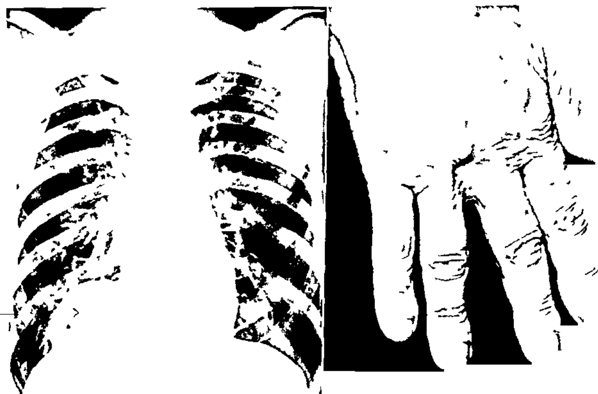


Figure 1 … of fingers A (*Left*) Round well circumscribed
density … mass to be situated posteriorly adjacent to the
spine) … ration a peripheral tumor was found histologically
… inoma)

the posterior portion of the pituitary neural unit. In each instance the primary disease was a bronchiogenic carcinoma.

These observations may find a common denominator in the action of the pituitary gland on the vascular and hemopoietic systems. In a study of the interrelationship between the lungs and the pituitary gland Moehling concluded that diseases of the lungs, such as cancer (primary and metastatic), chronic pulmonary suppuration and pulmonary osteoarthropathy are often associated with pituitary chromophil hyperplasia. This author suggests that lung diseases produce an inflammatory reaction which calls for vascularization oxygenation and hemopoiesis and this process in turn results in a compensatory hyperplasia of the pituitary chromophil cells. It is noteworthy that animal experiments have shown a close relationship between the pituitary gland and the development of tumors. Removal of the pituitary suppresses the growth of cancer. The current use of hormonal treatment of malignant disease of the prostate and breast with stilbesterol and testosterone, respectively, is essentially a form of "medical hypophysectomy."

As for the direct agents involved in the production of digital clubbing, it is generally believed that the latter is due to hypertrophy and hyperplasia of tissues caused by increased blood flow and nutrition of the affected parts resulting in minute arteriovenous anastomoses. Charr and Swenson demonstrated, by means of infra-red photographs of living persons and also postmortem arteriograms, that the local vascular bed is increased and widened in cases of clubbing. This is assumed to indicate an increased peripheral blood flow. An accompanying low tissue oxygen tension may be a contributing factor. This mechanism can also be demonstrated in unilateral digital clubbing associated with arteriovenous fistula. In two cases of unilateral clubbing, one following trauma of the right limb and the other congenital in origin, Wilson found an excess of blood flow of the affected parts. As was mentioned previously, the successful treatment of pulmonary lesions associated with joint pains and clubbing may lead to a return of the fingers to a more normal appearance. In most instances, the disappearance of clubbing after operation is more apparent than real. There are few objective studies on record documenting such transformations.

Diabetes and Pulmonary Infections

Physiological Considerations

Diabetes favors infection of the lungs as it does of the skin, kidneys and other parts of the body. The reason for the vulnerability of the diabetic to infection is not entirely clear. For a time it was believed that the increased sugar content of the blood provides a medium favoring the growth of microorganisms. As is well known, the addition of glucose to culture media enhances the growth of the tubercle bacillus, yet, pyogenic organisms do not grow better in vitro in a blood sugar medium than in a blood medium alone. But if the blood is obtained from a patient in a diabetic coma certain bacteria do grow better. More weight is ascribed to faulty metabolism of the tissues. Dogs rendered diabetic by pancreatectomy show a greater degree of inflammatory necrosis of the skin than do the controls (Horster). Likewise, depancreatized dogs show increased susceptibility to infection with the tubercle bacillus (Steinbach and others). The predisposition of patients with prolonged pancreatic insufficiency to infection is strikingly demonstrated in the massive necrotizing pneumonias encountered in patients with pancreatic lithiasis (Moolten). Similar factors may be at play in infants and children with pulmonary infections associated with cystic fibrosis of the pancreas to be described shortly.

The aforementioned studies would indicate that the susceptibility of the diabetic to infection is due in part to faulty carbohydrate metabolism caused by absence of islet-cell secretion (insulin). In addition, there may be unexplained weaknesses within the lung structure itself. Root and Bloor made chemical analyses of lungs removed at autopsy from diabetics. They found strikingly lower concentrations of phospholipid

and lipid than in nondiabetic patients Additional factors which may favor pulmonary infections in the diabetic are vitamin A and C deficiencies endocrine disturbances and lowered local resistance due to vascular damage of tissues

Infection is particularly serious in the uncontrolled diabetic because of the associated starvation dehydration and other conditions resulting in ketosis Dubos found that infection in the diabetic is facilitated during ketosis by the additive effect of two factors (1) the presence of ketone bodies in abnormally high concentrations, and (2) the decreased production of lactic acid at the site of inflammation Lactic acid inhibits and ketone bodies stimulate the multiplication of staphylococci and tubercle bacilli at the acid reactions which usually prevail in inflammatory areas This may explain in part the susceptibility to infection which is often associated with ketosis of various etiology

Diabetes and Pulmonary Tuberculosis

The diabetic is particularly vulnerable to the development of tuberculosis which is apt to be in an advanced stage and acutely progressive when first discovered A survey conducted in Philadelphia begun in December 1945 and concluded in 1947 revealed twice as much tuberculosis in diabetics as in a comparable group of nondiabetics and three times as much *active* tuberculosis A direct correlation could be shown between the increasing severity of diabetes and the increasing prevalence of active tuberculosis These findings substantiate what has long been known regarding the two diseases Previous estimates of the prevalence of tuberculosis in diabetics had been somewhat higher but clear cut distinctions had not always been made between active and inactive disease The lower figures in the Philadelphia survey reflect also the considerable decline in the incidence of tuberculosis in recent years The death rate from diabetes had shown relatively little change during the same period

Recently published statistics from the Joslin Clinic are particularly significant They reveal that early in the present century tuberculosis accounted for approximately 5 per cent of the deaths among the diabetics in the Joslin Clinic between 1950 and 1952 the percentage fell to 0 9 per cent In the population at large during the same period the incidence of deaths due to tuberculosis among diabetics was considerably higher But in spite of the improved picture tuberculosis still remains one of the most serious complications encountered in diabetes particularly in uncontrolled diabetes

The following data which I gathered at the Montefiore Hospital some years ago is in basic agreement with the reports cited In a study of seventy two elderly tuberculous diabetics the diabetes usually preceded the appearance of symptoms of tuberculosis But there was reason to believe that in many instances probably the majority a latent tuberculous focus had been present prior to the diabetes After the development of the diabetes an acute exacerbation of the latent tuberculosis took place Occasionally one obtained a clear cut history of active tuberculosis brought to arrest and after the development of diabetes the occurrence of a relapse At the present time with better means of controlling tuberculosis increasing numbers of individuals reach the diabetic age thereby affording greater opportunities for later reactivation of their tuberculosis Since the introduction of isoniazid in the treatment of tuberculosis I have encountered a number of patients in whom there was reason to suspect that possibly the medication itself may have been instrumental in reducing the sugar tolerance in susceptible individuals to a point where frank diabetes appeared This problem requires further study

Much has been written of so called diabetic phthisis which is featured by a relative paucity of physical signs in contrast to the extensive caseation necrosis of lung tissue a predilection of the disease for mid zonal and basal regions a comparatively slight pleural reaction a low incidence of extrapulmonary tuberculosis and a greater tendency to pulmonary hemorrhage In older individuals in whom one expects to see a predominantly fibrotic tuberculosis unusual manifestations of the disease such as those mentioned are apt to be particularly impressive These and other features of diabetic phthisis

may be related with the manner of onset and spread of the tuberculous process, the adequacy of the diabetic control as well as the age groups involved Reactivation of a tuberculous process in a middle-aged person is apt to be from a subapical and parahilar focus, often initiated by ulceration of a caseocalcarious lymph node into a regional bronchus. Excessive amounts of liquid sputum and recurring hemoptyses favor spread of the disease to the lower lobes In an uncontrolled diabetic who had lost considerable weight and is possibly in acidosis, the resulting aspiration infection is all the more serious However, in the majority of tuberculous diabetics, especially those encountered in general surveys and in private practice, one meets with inactive tuberculous foci in the upper lobes and so-called, "diabetic phthisis' of the type previously described is the exception Nevertheless, tuberculosis in an elderly individual, in whatever form the lung disease takes, should bring to mind the possibility of a latent diabetes and the patient examined for the presence of excess sugar in the blood and urine

It is not within the scope of this discussion to enter into the treatment of the tuberculous diabetic Suffice it to mention that with the availability of potent antimicrobial agents the tuberculous diabetic has now an excellent chance of having his disease brought under control Pneumothorax has been practically abandoned in the tuberculous diabetic, in fact, pneumothorax is rarely indicated even in the nondiabetic Because of the unusual severity of the tuberculous process it is advisable to utilize the most potent antituberculosis agents available as soon as the diagnosis of active tuberculosis is made, including streptomycin, para aminosalicylic acid (PAS) and isoniazid Since elderly individuals are apt to be intolerant to PAS, one uses preferably a combination of streptomycin and isoniazid The underweight diabetic needs a high caloric diet, rich in carbohydrates and low in fat Insulin is necessary to cover the excess of caloric intake Occasionally especially in the younger age groups, resection finds indications In the management of the diabetic it is incumbent on the physician to take periodic x-rays of the chest in order to discover tuberculosis in its earliest and most curable stages

Diabetes and Nontuberculous Pulmonary Infections

Although there are no reliable statistics of the incidence of nontuberculous pulmonary infections in diabetics, as compared to nondiabetics, experience teaches that acute pneumonias, pulmonary suppurations, fungous as well as spirochetal infections, when they occur in the uncontrolled diabetic, are apt to be especially severe and take on massive proportions Suppurative pneumonia, almost invariably associated with abscess formation, is frequently encountered in the diabetic "Diabetic gangrene of the lung" and "diabetic pneumomalacia," well known to previous generations of physicians, are pungent descriptions of the condition (Figure 2)

Suppurative pneumonias and lung abscesses find fertile soil in the diabetic with poor mouth hygiene, pyorrhea and carious teeth, especially if the cough reflex and cleansing mechanism of the upper air passage are interfered with or suppressed, thereby allowing ingress of bacteria into the deeper recesses of the lungs In the exceptional case there may be pulmonary abscesses caused by hematogenous implantations of infected emboli from distant foci (*see* Chapter 10) In many instances, aspiration infections follow operative procedures in the oral cavity or in other parts of the body under general anesthesia Temporary loss of consciousness during coma or alcoholism or after deep sedation and shock treatment, are additional causes Preexisting pneumonitis, bronchial asthma and advanced age are contributing elements Of prime importance is the condition of the vascular bed The presence of considerable degrees of atherosclerotic and occlusive endarteritic changes of the blood vessels favors massive pulmonary necrosis Tuttle and Nicoll found that ligation of the pulmonary artery in the dog had a markedly deleterious effect on a beginning lung abscess, increasing the extent of involvement, limiting pyogenic membrane formation and sometimes causing gangrene of a lobe

In some patients the disease is characterized by

fetid sputum indicative of an infection with a multiplicity of microorganisms including spirochetes and other anaerobic bacteria In others, the disease is associated with nonfetid sputum Smith found that although single strains of anaerobic organisms do not produce disease, when present in combination they act in symbiosis and produce gas, fetid odor and greenish pus It may be difficult to determine whether or not the suppuration is of the, so called putrid or non putrid variety since one may merge into the other Under the effects of antibacterial medication sputum elimination is quickly suppressed and loses its offensive odor The particularly bad prognosis at one time associated with suppurative pneumonia and lung abscess in the diabetic has lost much of its grave import since the introduction of penicillin and other antibacterial agents But the combination is still a serious challenge

After institution of antibacterial medication and bronchoscopy to help cleanse the air passages also postural and supportive measures, the disease clears in a few weeks, occasionally months Surgery at the present time has relatively few indications Resection finds a place in the treatment of chronic lung abscesses which fail to resolve under medical treatment or a persisting focus which may have antedated the acute exacerbation of the disease But it should be emphasized that the mere amelioration of symptoms and apparent clearing of a lung abscess does not necessarily indicate eradication of the disease Under the effects of penicillin the massive area of necrosis rapidly diminishes in size but a ring shadow may persist and at times be hardly discernible in the chest x ray The annular shadow represents a thin walled cavity, possibly associated with obstruction of the draining bronchus Before an abscess can be considered healed sectional radiography is essential Incidentally, similar ring' shadows are also being encountered with some frequency in pulmonary tuberculosis treated with antituberculosis agents, especially isoniazid The excised specimen shows a smooth

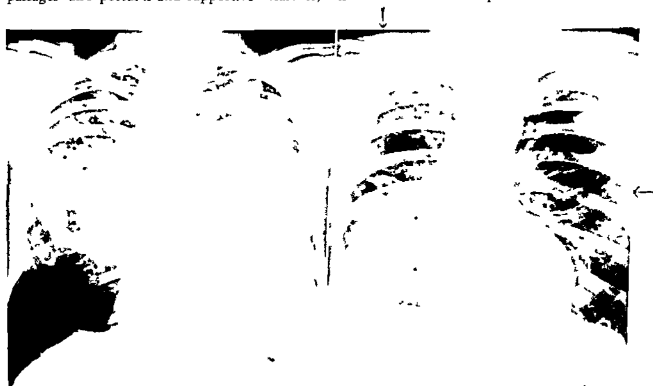


Figure 2 Suppurative pneumonia in a diabetic A (Le[ft]) ... lidation in ... of
the right lung scattered areas of highl ... (Right) ...
with residual thickening of interlobar f... with
tural ... su

glistening lining and in many instances no evidence of tuberculous granulation tissue can be demonstrated

The roentgen features of nontuberculous pulmonary infections in the diabetic differ little from those found in the nondiabetic excepting for the greater tendency in the former to cavity formation In acute disease the affected lung may show multiple fluid levels indicative of rapid breakdown of tissues It might be mentioned that in general the presence of fluid levels in multiple cavities is more in keeping with nontuberculous rather than tuberculous infection The diagnosis depends on the presence or absence of acid fast bacilli in the sputum A giant cavity may occupy the major portion of a lung simulating a pyopneumothorax The latter may coexist as a result of rupture of an abscess into the pleural cavity

Cystic Fibrosis of the Pancreas and Pulmonary Infections

Introduction

Fibrocystic disease of the pancreas has been a popular subject of discussion in pediatric literature since 1938 when Dorothy Andersen also Blackfan and May drew attention of physicians to the condition Cystic fibrosis of the pancreas when it occurs is a hereditary disease and follows recessive Mendelian characteristics The disease is an important cause of death in infancy and early childhood and is found in some statistics in as high as five per cent of autopsies of the young With increasing awareness of the possible existence of cystic fibrosis of the pancreas the condition is now being recognized also in older children Pugsley and Spence reported the case of a seventeen year old boy with cystic fibrosis of the pancreas associated with chronic pulmonary disease and cirrhosis of the liver Among 375 cases studied di Sant Agnese included one nineteen years old

Etiology

Based on studies by Blackfan and Wolbach also Farber and others it has long been known that fibrocystic disease of the pancreas is part of a generalized disease Farber coined the term mucoviscidosis to describe this constitutional inadequacy which manifests itself in an abnormal secretory mechanism involving mucous glands The obstruction of gland ducts by viscid mucus leads to atrophy and fibrosis of the organ According to di Sant Agnese the condition involves perhaps all exocrine glands chiefly those of the pancreas lungs liver sweat and salivary glands This investigator believes that in the young this disorder accounts for virtually all cases of pancreatic deficiency for a majority of those with chronic (nontuberculous) lung disease and for one third of children with cirrhosis of the liver and portal hypertension Noteworthy is the fact that abnormal sweat electrolyte concentration may lead to massive salt depletion and death

In support of the generalized nature of mucoviscidosis Zuelzer and Newton found that of twenty eight children with cystic fibrosis of the pancreas examined at autopsy 85 per cent had changes in the gastrointestinal tract consisting of dilatation of glandular structures with mucus and atrophic flattening of the lining cells Next in frequency were changes in the biliary passages which were noted in 60 per cent of the cases The gallbladder of those affected were small shrunken gray in color with thickened walls and an almost solid opaque stringy colorless mucus filling the lumen In keeping with this theory the pathologic process in the respiratory tract is assumed to be analagous to that in the pancreas and in other glandular organs When pancreatic insufficiency is caused by a lesion which is local in character no pulmonary changes are found When the pancreatic insufficiency is part of a generalized disease the lungs are usually involved and in a characteristic manner as will be described presently

When cystic fibrosis of the pancreas was first recognized many were of the opinion that nutritional factors were primarily or largely responsible for the pulmonary changes Andersen and her associates believed that as a result of

nutritional insufficiency and failure of the infant to absorb sufficient amounts of vitamin A, the respiratory epithelium becomes susceptible to infection and this results in suppuration, fibrosis, bronchiectasis and other changes Current thought is that nutritional deficiencies play a secondary, though clinically important, role in the evolution of the pulmonary changes Although squamous metaplasia of respiratory epithelium can be produced by vitamin A deficiency, a causal relationship cannot be established because metaplasia is not a constant feature and is not found in the absence of infection Zuelzer and Newton point out that metaplasia of *epithelium may occur in association with chronic* inflammatory lesions in patients with normal pancreatic function whose intake and absorption of vitamin A are presumably adequate Futhermore the administration of vitamin A does not improve significantly the pulmonary disease

Clinical Features

Fibrocystic disease of the pancreas presents a clinical picture not unlike that seen in celiac disease As in the latter, the infant shows wasting, abdominal distention and eliminates bulky fatty, foul-smelling stools But in contrast to celiac disease, for which no cause has been found, fully developed fibrocystic disease of the pancreas reveals histological changes of the organ consisting of dilated acini, the ducts containing variable amounts of coagulated mucinous substance There is diffuse connective tissue formation in the gland but no actual inflammatory reaction and the islands of Langerhans are spared Dietetic treatment is of little avail and the infant succumbs *in a few months, or at most, a few years* usually of a superimposed pulmonary infection

It would take us too far afield to discuss the laboratory diagnosis of the *disease except to point* out that among the more important tests are the examination of the duodenal contents for lipase, amylase, and trypsin which are *markedly* decreased or absent in pancreatic [illegible] fibrosis The proteolytic power of the [illegible] tested by a simple method, suggested [illegible] A piece of gelatine film (unfixed [illegible] is placed in a mixture of stool and [illegible] tube and incubated in a test pc [illegible] thirty minutes If the stool is positive for trypsin the gelatine of the film is digested and shows clearing False positive tests can be obtained Hirsch and *co workers devised a pancreatic* function test by measuring the postprandial rise in esterified fatty acids of the blood Healthy children show an increase of such acids between thirty two and more than 200 per cent after test meals In contrast, children with fibrocystic disease of the pancreas show slight, if any, postprandial increase This indicates a failure of fat absorption from the bowel and reflects a disturbance of pancreatic function Excessive fat in the stools is examined by the Sudan stain In addition *to the aforementioned, one obtains* low cholesterol values and low vitamin A values as a result of poor absorption of fat

A test which promises to be of considerable value, as a screen in the detection of fibrocystic disease of the pancreas, has been recently introduced by Silverman and Shirkey The test depends upon the fact that iodized fat (lipiodol) is digested and absorbed by normal children and the iodine is subsequently excreted in the urine in high concentration In contrast, children with fibrocystic disease of the pancreas, whose digestion of fat is impaired have a diminished urinary output of iodine The test is quantitative as well as qualitative The "sweat" test is becoming an important means of diagnosing fibrocystic disease of the pancreas Studies carried out at the Babies Hospital, New York, have shown that children with this disease consistently exhibit a specific abnormality of sweat electrolytes Sweat chloride and sodium are increased two to four times above the concentration found in controls Of particular interest is the fact that in some of the apparently healthy relatives of the patients a sweat electrolyte pattern was found characteristic of the disease

According to Andersen and others who have studied [illegible] 'ers of cases, children with fibrc [illegible] of the pancreas fall into one of three [illegible] oups (1) a neonatal group in which [illegible] within the first week or two of life [illegible] accumulation of nonliquified meconi [illegible] to failure of [illegible] This leads to [illegible] in the

region of the ileocecal valve with resulting proximal dilatation of the gut and death (2) A group in which death occurs between the neonatal period and six months of age from respiratory tract infections, although failure to gain weight and other evidence of the celiac syndrome may also be present, and (3) a group which survives longer than six months in which the initial symptoms are chiefly abdominal but symptoms referable to the respiratory tract soon become increasingly more pronounced eventually leading to a fatal issue Of special interest from the viewpoint of the present discussion is the fact that fibrocystic disease of the pancreas is usually associated with pulmonary infection In almost all 325 patients di Sant Agnese found pulmonary involvement of varying degree at some time in the course of the illness The respiratory disease was severe and accounted for over 90 per cent of the 145 deaths

Pathological Features

The changes in the lungs are due primarily to obstruction of bronchi by viscid secretion which involve large as well as small channels If a major bronchus is involved it may lead to atelectasis of an entire lobe or several lobes Involvement of small bronchi leads to variable degrees of focal atelectasis and/or emphysema depending on the degree and extent of bronchial implication Sooner or later infection supervenes especially with hemolytic staphylococci leading to suppurative bronchitis and bronchopneumonia In long standing disease there is recurring pulmonary infection fibrosis bronchiectasis and emphysema

The pulmonary involvement is associated with progressive respiratory insufficiency leading to cor pulmonale if the child lives long enough Physiologic studies of pulmonary function in older children reported by West and co workers have shown a pattern of dysfunction which these investigators believe is characteristic of the disease but which is subject to considerable variation in severity They found both ventilatory insufficiency leading to dyspnea and disturbances in gas exchange leading to arterial hypoxia and carbon dioxide retention The pulmonary dysfunction is ascribed chiefly to the factor of obstruction of bronchi by secretions causing ventilatory impediment, also an uneven distribution of tidal air

Roentgenology

The roentgen findings reveal the various pathologic changes mentioned Early in the disease the bronchitic symptoms may not find expression in gross roentgen abnormalities but after repeated infections the presence of disease is revealed in accentuated perivascular and peribronchial markings located chiefly in the inner and midportions of both lungs In a study of 211 children with cystic fibrosis of the pancreas di Sant Agnese found that in approximately 10 per cent the chest x ray revealed massive atelectasis involving one or more lobes during the first episode of pulmonary involvement The right lung was found especially vulnerable, in fact, not a single instance of left sided atelectasis was encountered In advanced disease one finds patchy densities alternating with areas of highlight in keeping with the progressive consolidation emphysema and bronchiectasis Occasionally, the roentgen findings are sufficiently distinctive to suggest the nature of the underlying disease if the latter is not already known

Keats draws attention to the fact that pulmonary emphysema may be one of the earliest roentgenologic signs of cystic fibrosis of the pancreas The emphysema is usually irregular in distribution but may involve both lungs diffusely and to a marked degree The emphysematous stage is transient and soon gives way to atelectasis and signs of infection

Case 1 Female—Age Infant

Had repeated respiratory infections shortness of breath and rattling in the chest since shortly after birth. At the age of seven months the infant was hospitalized because of inability to gain weight malodorous bulky stools fever cough and vomiting A diagnosis of cystic fibrosis of the pancreas was made Chest x rays revealed exaggerated bronchovascular markings and linear infiltrations involving chiefly the left upper lobe

After a five-month period of improvement under antibiotics the infant was readmitted to the

hospital because of aggravation of symptoms The chest x ray now revealed patchy and linear infiltrations in the right lung as well as progressive changes in the left (Figure 3) Further tests confirmed the presence of cystic fibrosis of the pancreas The infant was treated with various antibiotics and for a time gained weight but soon sustained a relapse developed acute respiratory symptoms and died at the age of twenty six months Autopsy revealed diffuse fibrosis and bronchiectasis with areas of bronchopneumonia in both lungs also cystic fibrosis of the pancreas

Krabbenhoft and Evans have drawn attention to the fact that infants with intracardiac septal defects may show pulmonary changes similar to those seen in cystic fibrosis of the pancreas As in the latter the authors found variable degrees of pulmonary atelectasis and/or emphysema Although infants with congenital heart disease do not exhibit abnormally viscid mucus of the degree encountered in mucroviscidosis excessive amounts of mucus were observed in several of the cases In considering these findings along with other pulmonary manifestations of infection the authors believe that serious thought should be given to both conditions in differential diagnosis

The scope of this book does not permit the inclusion of details of treatment But, it might be mentioned that in addition to dietary measures including high protein high calorie and slightly reduced fat intake also large doses of vitamin especially A and D and pancreatic replacement the greatest advances of recent years have been in the field of prevention and treatment of pulmonary infection through the use of antibacterial agents Frequent sensitivity tests of the microorganisms obtained from the upper air passages and sputum are necessary to make certain that the particular antibiotic or combination of antibiotics is effective

Stoppelman and Schwachman reported observations on 140 patients with mucoviscidosis treated with antibiotics at the Children's Medical Center Boston Mass for periods as long as six years Children with mild pulmonary involvement received continuously chlortetracycline or oxytetracycline alone, in average doses of less than 20 mg daily per kilogram of body weight Patients with moderate to extensive pulmonary involvement received a combination of agents such as sulfadiazine, chloramephenicol, or erythromycin in addition to chlortetracycline or oxytetracycline Those with extensive pulmonary involvement were usually given penicillin or streptomycin aerosol therapy in short courses for

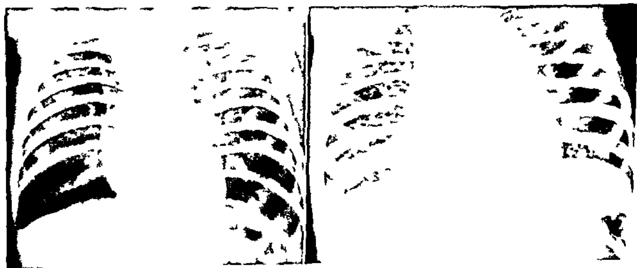


Figure 3 *Case 1* Cystic fibrosis of the pancreas associated with pulmonary fibrosis and bronchiectasis A (*Left*) Exaggerated hilar markings and linear infiltrations in the left upper lobe B (*Right*) Four months later marked increase in infiltrations in both lungs (Autopsy showed diffuse pulmonary fibrosis and bronchiectasis also areas of bronchopneumonia cystic fibrosis of the pancreas)

two or three weeks and rarely for longer periods The relation of such prolonged treatment to changes in bacterial flora and the occurrence of antibiotic resistance was studied It was found that, despite the appearance of antibiotic resistance in the nasopharyngeal flora of these patients, a satisfactory clinical response could still be obtained

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Chapter 3

Diseases of Metabolism (Concluded)

Histiocytosis with Pulmonary Involvement

Introduction

THE HISTIOCYTE is a large pale foam cell found in the reticuloendothelial system from which are derived the epithelioid and giant cells of certain inflammatory processes Among diseases of the histiocytic or reticuloendothelial system two major disorders are recognized one metabolic, the other inflammatory The metabolic histiocytoses Gaucher s disease and Niemann Pick s disease are rare heredofamilial diseases found almost exclusively in the young and characterized by the deposition of specific lipids in the cells In Gaucher s disease the lipid is a cerebroside in Niemann Pick s disease the lipid is a phosphatid These two are storage diseases the lipids being present within the cells but not in the blood The inflammatory histiocytoses although encountered chiefly in the young are also seen in older persons The diseases are characterized by eosinophilic granulomatous changes in various organs and tissues of the body The inflammatory histiocytoses are Hand Schuller Christian s disease Letterer Siwe s disease eosinophilic granuloma of bone and on rare occasion eosinophilic granuloma limited to the lung Lightwood prefers the term histiocytic reticulo endotheliosis because it is still open to question whether the condition is inflammatory In line with this view Bodian speculates that these syndromes may be examples of histiocytic neoplastic processes varying from solitary or multiple focal lesions to a diffuse and frankly malignant disorder of the reticulo endothelial system

The inflammatory disorders of the histiocytic system differ in several respects from the primary lipid metabolic disorders In Hand Schuller Christian s disease there is often present an increase in cholesterol and cholesterol esters in the blood as well as in the tissues The increase in lipid content however is a secondary phenomenon and is encountered chiefly in advanced stages of the disease It is not a basic feature of the disease Letterer Siwe s disease is a nonlipid histiocytosis but an increase in lipid content may also be present in this condition Cases of Letterer Siwe s disease have been described in which the lipid content of the tissues was quite high although the disease had existed for only a short time Eosinophilic granuloma of bone may affect one several or many bones According to Jaffe and Lichtenstein who coined this term the condition represents the mildest expression of inflammatory histiocytosis Very few well documented cases are on record of eosinophilic granuloma limited to the lung

In the initial stages of the various inflammatory histiocytoses mentioned the pathologic changes may be quite similar but the clinical *manifestations* often show considerable variation and overlapping as exemplified in titles such as the following Reticulogranuloma Report of a Case of Eosinophilic Granuloma of Bone Associated with Nonlipoid Reticulosis of Skin and Oral Mucosa Under the Clinical Picture of Hand Schuller Christian Disease or Histiocytic Granuloma of Skull (Triphasic Clinico Pathologic Syndrome Previously Termed Letterer Siwe s Disease Hand Schuller Christian Disease and Eosinophilic Granuloma) The several forms of inflammatory histiocytoses apparently represent different facets of a single disturbance At one extreme usually seen in infancy one

meets with acute forms of Letterer Siwe's disease, at the other, one meets with chronic, localized eosinophilic granuloma of bone encountered more often in older persons Intermediate, subacute and chronic variants are seen at all ages, especially in later childhood These are represented most often in Hand Schuller Christian disease The monistic concept of the reticulo endothelioses originally proposed by Wallgren, is subscribed to by most investigators in the field

To simplify the discussion, possibly at the expense of oversimplification, each disorder will be defined briefly and the pulmonary manifestations described for the group as a whole But before doing so, it is in order to mention a form of lipid pneumonia characterized by interstitial fibrosis and, histologically, by the presence of foamy monocytes containing cholesterol The underlying cause in the majority of cases is tissue injury although distinct evidence of the latter may not be apparent This type of localized lipid-filled granuloma is not demonstrably part of a systemic disease There is reason to suspect, however, that in some cases it represents an abortive form of a basically widespread disease

Endogenous Lipid Pneumonia

In this condition, fatty changes, consisting largely of cholesterol and its esters, are found in association with chronic degenerative pulmonary diseases The amount of fat demonstrable histologically varies in different pathological states It is not found in acute pulmonary disease but is present in varying amounts in tuberculosis, chronic bronchiectasis, chronic abscesses and, most often, in association with carcinoma of the lung In the presence of a major underlying disease, such as those mentioned, the lipid changes are of incidental interest But when the lipid deposition dominates the picture or when the nature of the underlying disease is not readily ascertainable, the finding of massive deposits of fat in the tissues provokes speculation Endogenous lipid pneumonia a term suggested by DeNavasquez and Haslewood, is also known as "cholesterol pneumonia," "foam cell pneumonia 'chronic pneumonitis of the cholesterol type" and by several other nomenclatures

The lack of a precise definition of the condition is an index of its ill-defined nature Although endogenous lipid pneumonia is to be distinguished from oil aspiration pneumonia, due to excessive intake of mineral oil or oily nose drops by persons with defective cough reflexes, a sharp distinction is not always possible In fact, there is reason to believe that many of the reported cases of endogenous lipid pneumonia represent, in reality instances of oil aspiration in patients in whom a sufficiently detailed history is not obtainable Davis cited six cases who, at operation were found to have "localized" or "segmental" lipid pneumonia Before operation the diagnosis was carcinoma Three of the patients gave a history of ingestion of large quantities of mineral oil for constipation One patient had a long history of the use of oily nose drops and one patient, a high altitude aviator, used petroleum jelly around his nose and mouth to make the mask fit better The sixth patient, for want of a history of oil aspiration, fitted into the group of endogenous lipid pneumonia Recently a patient was treated at the Montefiore Hospital in whom a lipid pneumonia caused a localized granuloma simulating a neoplasm But only after the mass was excised and the tissue showed a gelatinous tumor with lipid laden macrophages was a history obtained that the patient had been using oily nose drops for many years

Robbins and Sniffen reported eleven cases of 'chronic pneumonitis of the cholesterol type treated surgically The outstanding feature of the pneumonia was the presence of deposits of cholesterol and cholesterol esters in the air spaces, in the absence of coexistent lung disease The evidence did suggest, however, that some obstruction of the smaller bronchi or bronchioles was often present and that this might have been a determining factor in laying the background for the type of reaction observed Five years later Waddell, Sniffen and Whytehead concluded that the endogenous variety of lipid pneumonia is due to local acidosis in an injured or infected tissue causing an adverse effect upon the colloidal lipids They found that in rabbits the intratracheal inoculation of either Pasturella pseudotuberculosis or Klebsiella pneumoniae resulted in

interstitial pneumonitis in which large numbers of macrophages were seen. In the presence of induced lipemia and hypercholesterolemia these cells became laden with cholesterol and fat producing the picture seen in humans. According to these investigators endogenous lipid pneumonia and aspiration lipid pneumonia may be distinguished by the fact that the microscopic picture in the former shows a uniform distribution of lipid throughout the cytoplasm of the macrophages and the droplets are extremely minute.

Of particular interest is the fact that the roentgen changes of lipid pneumonia whether endogenous or exogenous may resemble closely those of primary pulmonary neoplasm as illustrated by the following case.

Case 2 Female—Age 50

The patient became ill in March 1953 with cough, expectoration and wheezing. She stated that she seldom had coughed previously. There was no fever, shortness of breath, hemoptysis or chest pain. The patient did have a sense of soreness over the right upper chest and had lost a moderate amount of weight. The past history was unrevealing. She had been a light smoker and used nose drops on rare occasions. She had no difficulty in swallowing and had no major operations.

The physical and x-ray findings of the chest revealed a dense homogeneous consolidation occupying the entire right upper lobe (Figure 4A). Bronchoscopy showed stenosis of the right upper lobe bronchus. Smears taken failed to reveal tumor cells or acid fast bacilli. On July 21, 1953 an exploratory thoracotomy was done by Dr. Morris Rubin. The right upper lobe was found completely consolidated; the middle and lower lobes were free of disease. There were enlarged hilar lymph nodes. The lesion appeared malignant and a right pneumonectomy was done which the patient tolerated well.

Gross examination reveals almost the entire upper lobe replaced by a firm tissue mass (Figure 4B). The lower lobe was collapsed and no areas of consolidation or increased consistency were found. The surface of both lobes was smooth and glistening. No adhesions were noted nor were there any interlobar adhesions. The bronchial tree contained some mucoid material but no evidence of tumor. The hilar

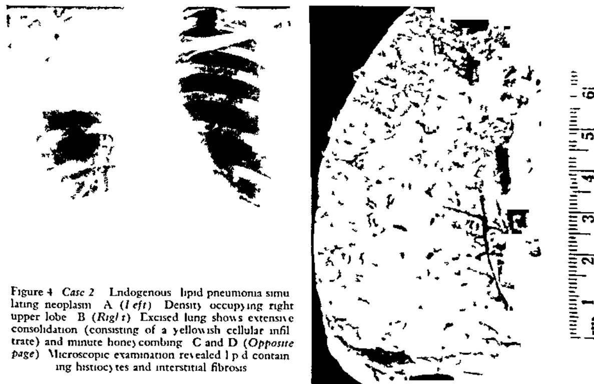


Figure 4. *Case 2.* Endogenous lipid pneumonia simulating neoplasm. A (*Left*) Density occupying right upper lobe. B (*Right*) Excised lung shows extensive consolidation (consisting of a yellowish cellular infiltrate) and minute honeycombing. C and D (*Opposite page*) Microscopic examination revealed lipid containing histiocytes and interstitial fibrosis.

lymph nodes were small, spongy and anthracotic On section, there was an extensive consolidation of the entire lobe The consolidation consisted of a yellowish cellular infiltrate through the parenchyma There was no evidence of tumor tissue seen anywhere in the lung Some of the consolidated areas were softer in consistency and revealed areas of necrosis The microscopic findings confirmed the gross appearance of a lipid pneumonia (Figures 4C and D)

Recently I had an opportunity of demonstrating that the finding of a lipid pneumonia does not necessarily imply an irreversible reaction A man of fifty-eight presented himself with a six-month history of cough, malodorous but not distinctly foul expectoration, loss of thirty pounds in weight, pain in the right chest and weakness The past history revealed a seizure of influenzal pneumonia after World War I and periodic recurrences of hay fever and hives The patient had considerable cough and moderate dyspnea during the preceding five years. The physical examination was not revealing. The chest x-ray showed a large, fairly well circumscribed density in the right upper lobe Bronchoscopy revealed a number of atypical cells. In the absence of a clear-cut history to suggest pulmonary suppuration, carcinoma was suspected and thoracotomy done

Upon entering the pleural cavity, a moderately hard mass was found in the right upper lobe It was densely adherent to the chest wall over a wide area Mobilization, even along an extrapleural plane, was not feasible It was felt that the mass was malignant and that a radical excision was too formidable an operation for the patient to tolerate. A piece of tissue was removed from the mass for histologic study The lung biopsy revealed severe fibrosis of the pulmonary parenchyma with whorls and nodules of fibrous tissue, also thickening of the alveolar septa Very

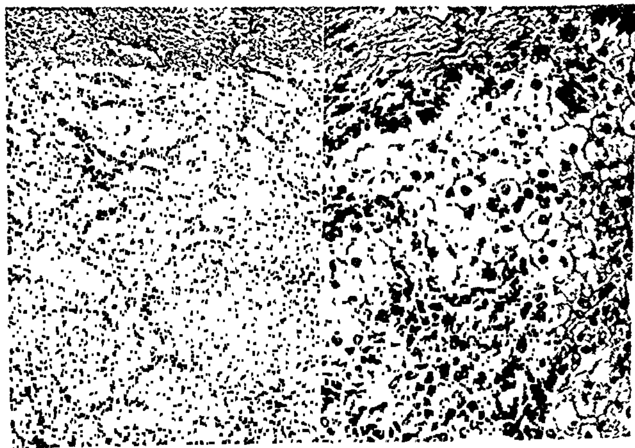


Figure 4C and D (See legend on p[illegible]

prominent were numerous groups of large vacuolated foam cells containing one or two small, round nuclei These cells were closely packed in clumps and appeared to be located in the alveolar lumens They represented large lipid filled macrophages The picture was in keeping with lipid pneumonia with organization There was no evidence of neoplasm

The patient was placed on intensive antibiotic treatment During the following eight months there was slow but steady decrease in the size of the mass and the patient made a parallel degree of symptomatic improvement with gain of forty pounds in weight I have encountered two additional patients who revealed at operation, apparently nonresectable pulmonary carcinomas Lung biopsies revealed lipid pneumonia and fibrosing pneumonitis The subsequent course of events in both cases extending over three and nine-year periods, respectively excluded the possibility of malignant neoplasms

Gaucher's Disease

This is a rare familial condition characterized by the accumulation of kerasin, a cerebroside in the cells of the reticuloendothelial system In a study of twenty nine cases by Medoff and Bayrd the ages ranged between two and one half and fifty six years at the time of the first visit to the Mayo Clinic The, so called Gaucher cells appear as wrinkled swollen reticular cells infiltrated with lipid found chiefly in the spleen liver lymph glands and bone marrow The clinical features of Gaucher's disease are an insidious onset, a protracted course with hepatosplenomegaly but normal liver function pingueculae, a yellowish brown pigmentation of the skin and sclera and skeletal defects especially of the femora and other long bones Hypochromic anemia, leukopenia thrombocytopenia and a tendency to hemorrhage are associated phenomena

Niemann Pick's Disease

This is also a rare metabolic disturbance occurring chiefly in Jewish female infants Except for the more widespread involvement and gastro intestinal disturbances leading to marked malnutrition, the condition resembles closely Gaucher's disease Death occurs usually before the age of three years from cachexia or an intercurrent infection In Niemann Pick's disease there is marked physical and mental deterioration, the latter akin to that met in Tay-Sachs amaurotic idiocy The lipid found in the tissue and which is pathognomonic of the disease is sphingomyelin a phosphatid The following report of a patient treated at the Montefiore Hospital is of unusual interest since it concerned an adult with lipidosis, closely resembling Niemann Pick's disease

Case 3 Male—Age 53

White Jewish patient was rather dull backward and sickly as a child and did not speak until he was seven years of age The patient was admitted to the Montefiore Hospital on December 7/51 with a history that ten months previously he developed weakness easy fatigability and a hacking cough productive of moderate amounts of sputum, at times blood tinged The patient soon developed dyspnea and orthopnea and on several occasions he had substernal pain which radiated to the left shoulder The dyspnea cyanosis increased and there soon appeared hepatosplenomegaly and evidence of cardiac failure X rays of the chest showed diffuse pulmonary fibrosis (Figures 5A and B) Biopsy of a lung specimen revealed collections of intraalveolar foam cells A complete study including various laboratory tests was unrevealing The patient continued to have cough productive of tenacious sputum at times bloody, and left sided chest pain. The patient became increasingly more dyspneic cyanotic stuperous lapsed into coma and died

The postmortem findings revealed, in brief massive involvement of the lungs liver and spleen by lipid filled histiocytes (Figures 5C and D) Relatively fewer of these cells were found in the adrenal corteses bone marrow and lymph nodes An abnormal pigment was found in these organs as well as the th[illegible]
ical [illegible]
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ease The large increase in phosphosphingoside pointed to Niemann Pick's disease Although large accumulations of this lipid were found in the liver and spleen, it was in smaller concentration than that noted by others in the tissues of infants with Niemann Pick's disease It was concluded that the lipidosis in this patient was related to Niemann Pick's disease though not identical with it



Figure 5 *Case 3.* Histioc[illegible]l lesions A (*Upper left*) Diffuse, reticular striations throughout both lungs B (*Upper righ*[illegible]owing fine honeycombing of the organ C (*Lower left*) Lung The alveoli are filled by lipid-containing hi[illegible]iocytes and the septa are sclerotic D (*Lower right*) Lung The intraalveolar foam cells are apparent in this section (Similar histiocytes were found in the liver, spleen, adrenal cortices, bone marrow and lymph nodes, disease in keeping with Niemann-Pick's disease.) (From Terry, Sperry and Brodoff *Am J Path*, 30 263, 1954.)

Hand Schuller Christian's Disease

This metabolic disturbance is characterized by yellow granulomatous nodules in the skin mucous membranes and internal organs. In a review of eighty four reported cases of Hand Schuller Christian's disease, Gross and Jacob noted that in twenty six the presence of foam cells was not mentioned and in nine necropsy and biopsy material showed no foam cells. With chronicity the foam cells are replaced by fibrous which may or may not contain variable amounts of eosinophils. As mentioned an associated feature is cholesterol infiltration of the tissues. The disease begins insidiously in childhood but it may attack infants as well as aged. The classical triad found in Hand Schuller Christian's disease which distinguishes it clinically from other histiocytoses is a bizarre combination of exophthalmos due to retro orbital proliferation of granulomatous tissue diabetes insipidus due to pituitary gland involvement and cystic lesions in the skeletal system due to destruction of bones.

Case 4 Male—Age 35

In the course of a pre employment chest x ray patient was found to have symmetrical infiltrations throughout both lungs also prominence of the hilar shadows. The heart was normal in size and configuration. Sputum examinations failed to reveal acid fast organisms. Other laboratory tests were noninformative. In the absence of an occupational history a diagnosis of diffuse pulmonary fibrosis, etiology unknown was made. The patient was not seen until eight years later when he returned to the clinic complaining of general weakness and progressive shortness of breath and more recently slight cough and hoarseness.

Physical examination at this time revealed evidence of considerable loss of weight dyspnea after the slightest exertion and cyanosis of the lips and cheeks. Palpation of the scalp revealed in the right parietal region a slightly tender irregular area of depression of the osseous wall which the patient noted he had had for about a year. The neck veins were engorged. The liver was enlarged and there was slight pretibial edema. The chest x ray now disclosed extensive interstitial fibrosis throughout both lungs from apex to base. The heart was moderately enlarged with definite prominence of the pulmonic conus and enlargement of both ventricles (Figures 6A B and C). An x ray of the skull disclosed a large irregular area of bone destruction in the right parietal region (Figure 6D). Several small cystic areas of bone destruction were also found in the upper two thirds of the right femur also evidence of bone destruction in the left pubic bone and left femur.

Biopsy of the lesion of the right parietal bone revealed a general histologic pattern of a lipid granuloma of the skull consistent with Hand Schuller Christian's disease. The patient showed evidence of increasing cardiac decompensation and died. A complete autopsy was not obtained.

Letterer Siwe's Disease

This is a nonhereditary nonfamilial form of histiocytosis of unknown cause. One form appears to follow acute respiratory or other infections but this is probably an incidental or secondary occurrence. The disease attacks infants almost exclusively. With few exceptions the disease is acute with a rapid and fatal course. There is a generalized hyperplasia of the reticuloendothelial cells with small tumor formations in the spleen liver lymph nodes thymus skin and bone marrow showing hemorrhagic tendency. As a rule there is no lipid storage in the cells if present it is a secondary phenomenon. With chronicity the disease takes on many features of Hand Schuller Christian's disease with increasing deposition of cholesterol in the histiocytes. The outstanding clinical features are marked weakness irritability and a tendency to bleeding. The physical findings reveal hepatosplenomegaly lymphadenopathy localized skeletal tumors and progressive anemia.

Case 5 Female—Age 20 months

At six months of age the infant was first treated for chronic discharging ears, also a macular papular eruption of the skin. The condition improved but six months later the infant was readmitted to the hospital because of a recurrence of the skin ailment which was suspected to be a seborrheic dermatitis or tuberculid. A chest x ray revealed miliary infiltrations throughout both lungs especially the upper lobes (Figure 7A). In view of the fact that the infant's father had been treated for tuberculosis it was suspected that the infant had miliary tuberculosis. However the Mantoux test was negative

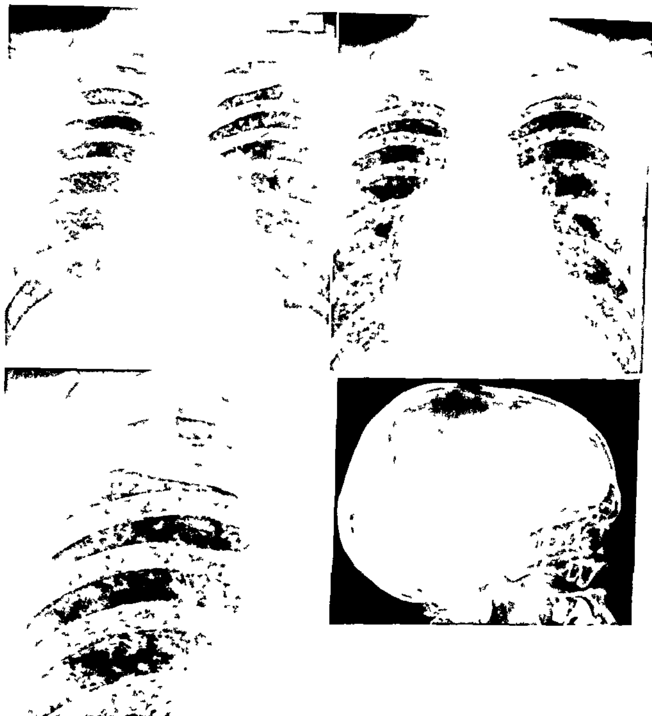


Figure 6 *Case 4* Histiocytosis with pulmonary and skeletal lesions A (*Upper left*) Diffuse reticular infiltrations throughout both lungs with minute cystic areas B (*Upper right*) Seven years later reticulations more conspicuous heart enlarged C (*Lower left*) Lung detail showing fine honeycombing D (*Lower right*) Skull Geographic defect of right parietal bone (Biopsy of parietal bone showed microscopically histiocytes foam cells and other features consistent with Hand Schuller Christian's disease) (From Schneierson and Schneider *Ann Int Med* 30 842 1949)



Figure 7 *Case 5* Histiocytosis with pulmonary and visceral lesions A (*Left*) Faint miliary stippling in both upper lobes B (*Right*) Five months later diffuse lace like reticulations with minute honeycombing of both lungs left sided pneumothorax (spontaneous) with catheter in situ (Autopsy showed histiocytosis of lungs with numerous blebs on surface histiocytosis of skin liver, spleen other features in keeping with Letterer Siwe s disease)

and repeated examination of gastric lavages and spinal fluid failed to reveal acid fast organisms At this time the liver and spleen were found to be enlarged, the cholesterol was 500 mgs % cholesterol esters 40 Other laboratory tests were noninformative The diagnosis was Hand Schuller Christian s disease

The infant was readmitted at the age of twenty months At this time there was found severe jaundice purpuric lesions of the scalp and seborrheic dermatitis cervical adenopathy and hepatosplenomegaly A liver biopsy was reported as showing cholangiectatic hepatitis A laparotomy revealed a dilated common bile duct but no hepatic obstruction The drainage from the abdomen was inadequate and shortly thereafter the patient had a left sided spontaneous pneumothorax which was decompressed with a drainage tube (Figure 7B) The course of the disease was progressively downhill and the infant died

At autopsy the liver was enlarged the common duct was dilated and there was a soft inspissated bile stone in the hepatic duct dilated bile ducts contained inspissated bile The lungs were airless with blebs on the surface The left lung was collapsed and revealed advanced consolidation of both organs The pleural surface of the right lung was smooth clear shining with numerous blebs on the surface The left lung was rough where an adhesion tore The cut section revealed airless solid lungs with numerous air cysts throughout also scattered yellowish areas Microscopic examination revealed elements of reticuloendothelial cells with histiocytes involving the skin liver and lungs Isolated histiocytes were found in the spleen Stains revealed fat-containing histiocytes in the liver and lung It was felt that the histologic picture was in keeping with Letterer Siwe s disease although there were features suggestive of a transitional stage between the latter and Hand Schuller Christian s disease

Eosinophilic Granuloma of Bone

Eosinophilic granuloma of bone is a granulomatous condition in which the affected bones contain large numbers of eosinophilic cells giving rise to cystic rarefactions The bone localization represents a limited form of inflammatory histiocytosis Jaffe and Lichtenstein, also Otani and Ehrlich believe that the condition represents a peculiar inflammatory reaction, the presence of lipid containing macrophages and fibrotic reaction being determined by the chronicity of the disease As mentioned eosinophilic granuloma of bone may be present in association with visceral involvements including involvement of the lungs Phillips reported two cases of intrathoracic 'xanthomatous' new growths and collected

three similar cases in the literature The tumors were solid firm oval and originated from the costovertebral groove of the thoracic cage They were nonmalignant The structure of the tumor was characterized by great abundance of lipid globules in large swollen polyhedral cells and smaller spindle shaped cells

Eosinophilic Granuloma of the Lung

In this disease pulmonary histiocytosis is present without demonstrable skeletal or visceral involvements The pulmonary lesion or lesions are found accidentally either at autopsy or on biopsy of lung tissue Lichtenstein suspects that such isolated pulmonary lesions of eosinophilic granuloma are accompanied by visceral lesions which are momentarily inapparent or may become manifest later Honeycomb lungs to which reference will be made later probably fall in the same category More perplexing is the differentiation between limited eosinophilic granuloma of the lung and endogenous lipid pneumonia described previously in which an accompanying disease or an obvious cause of tissue injury is not demonstrable In the condition under consideration it is presumed that the lipid accumulation in the lung is a forme fruste of a systemic disease But there is still much to be learned about this disease

In one type of eosinophilic granuloma of the *lung a solitary tumor mass is found which on* removal shows the histologic features of a histiocytosis Scott and co workers described such an occurrence in a thirty four year old woman The chest x ray had shown a circular circumscribed lesion in the right cardiophrenic angle A lung tumor was suspected and removed The mass was found to be the size of a large lemon completely contained within the lobe Histological examination revealed oval or spindle shaped cells with small groups of xanthoma cells There was no evidence of a generalized metabolic disturbance as manifested by diabetes hypercholesterolemia or lipemia There were no xanthomatous lesions in the skin and no osseous changes The authors believed that the tumor represented either an xanthomatous deposit of a primary nature or xanthomatous replacement of an underlying neoplasm with no identifiable remnants

Lieber and associates reported two histologically proved cases of eosinophilic granuloma limited to the lungs with somewhat unusual features In their cases the disease was bilateral diffuse and of a peculiar nodular quality Biopsy of lung tissue showed granulomatous lesions not sharply circumscribed showing fibrous tissue reaction pigment laden macrophages and histiocytes Eosinophils were a prominent feature being present as scattered individual cells as well as in sheets and in large clumps According to the authors the picture was that seen in eosinophilic granuloma of bone Two similar cases were reported by Mazzitello In one the chest x rays showed diffuse bilateral nodular infiltrations In the other the chest x rays revealed also numerous areas of rarefaction which were believed to represent multiple small cavities The presence of eosinophilic granuloma was confirmed in both cases by lung biopsies Of additional interest was the moderate degree of clearing of the pulmonary lesions with ACTH treatment

Pulmonary Lesions in the Histiocytoses

The pulmonary manifestations of diseases of the histiocytic system provide an interesting field of study from the viewpoint of the pulmonary findings The lungs often serve to highlight the *unified nature of the disturbance since com*parable and overlapping changes are present in the several forms of the disease Usually the lungs are implicated as part of a widespread disease but as mentioned the disease may be limited to or make its first appearance in the lungs In an analysis of eighteen reported cases of Letterer Siwe s disease Orchard found mention of pulmonary reticulosis in ten and in six others there were questionable changes Some years ago Chester and Kugel of the Montefiore Hospital compiled data on fifty reported cases of Hand Schuller Christian s disease including many instances in which the lungs were involved

In Gaucher s disease the lungs are seldom affected but when changes do occur they may be quite striking Myers reported the case of a young girl in whom the lungs showed roentgeno

logically delicate reticulations extending fanwise from the hilar regions into the mid portions of both lungs The child died and autopsy dis closed large hilar lymph glands and an infiltrative process extending into and invading the lungs Histological examination of the tissue revealed the lymph nodes and lung parenchyma perme ated with Gaucher cells Myers referred to an other reported case in which Gaucher cells were found in the sputum

In a lucid description of the pulmonary mani festations of Niemann Pick s disease Thann hauser draws attention to the frequency of bronchitic symptoms and the tendency to small pneumonic infiltrations associated with elevation of temperature The appearance of the chest x ray is in keeping with miliary tuberculosis Histologic examination of tissues reveal the bron chi filled with exudate containing leukocytes and Niemann Pick cells The interstitial tissues show accumulation of lipid Thannhauser believes that if it were possible to examine the sputum with the possibility of the existence of the disease in mind the diagnosis of Niemann Pick s disease might be made from the appearance of the cells alone

A brief note on treatment may be in order Although recovery is possible even in the acute forms of the disease the prognosis is usually poor except in cases of eosinophilic granuloma of bone which has a decided tendency to heal sponta neously Lightwood and Tizard found that of approximately forty reported cases of Letterer Siwe s disease there were six including one cited by these investigators in which apparent re covery took place Large tumor masses often respond to radiotherapy because the cells charac terizing this group of diseases are highly radio sensitive Steroid treatment has met with variable degrees of success Antibiotic treatment is indi cated because of the possibility that the symptoms may be partly due to infection to which the pa tients are unusually susceptible

Roentgenology of Pulmonary Lesions in Histiocytosis

From a review of a sizeable number of re ported cases of inflammatory histiocytosis in cluding a few personally observed it is possible to differentiate several roentgenologic patterns of the disease providing of course the basic dis turbance is known or suspected The cystic pattern to be described later may be sufficiently suggestive to make one think of the possible presence of a histiocytic disease in differential diagnosis in the absence of systemic lesions In Letterer Siwe s disease one is apt to see miliary or patchy infiltrations evenly dispersed in both lungs, especially the upper halves Occasionally large irregular consolidations are noted The former simulate miliary tuberculosis the latter bronchopneumonia There is often a remarkable similarity of the roentgen markings in Letterer Siwe s disease with those found in association with cystic fibrosis of the pancreas Since one is usually dealing with a disease of infancy the dif ferential diagnosis of the two diseases is always a consideration

In the chronic form of Hand Schuller Chris tian s disease one is apt to find linear fibrotic striations permeating both lungs The condition is in keeping with diffuse interstitial pulmonary fibrosis Hand Schuller Christian s disease may also manifest itself in small or large irregular den sities of granulomatous infiltration with hazy margins on a background of emphysematous lung tissue The picture brings to mind sarcoid osis although the latter rarely undergoes true cys tic changes rather emphysematous bullae and bleb formations Fungous infection is another disease that may be considered in the differential diagnosis As mentioned previously circum scribed lipid pneumonia may simulate neoplasms Inasmuch as the granulomas enlarge through in creasing deposition of lipid substance rather than cell division such xanthomas are not true neo plasms Instances have been described where it was suspected that the condition had undergone sarcomatous changes More likely as indicated earlier in the chapter the lipid changes are sec ondary to an underlying malignancy

Probably the most striking roentgen changes encountered in the inflammatory histiocytoses are cystic or honeycomb lungs Variable degrees of diffuse fibrosis of the organs are also present These small cysts usually not exceeding 1 cm in

diameter, are seen most often in patients with eosinophilic granuloma of bone The condition is also encountered in Letterer Siwe's disease as well as in Hand Schuller-Christian's disease In one of four cases, reported by Forsee and Blake, the chest x-ray showed bilateral air and fluid filled cysts, measuring 2 to 3 cm in diameter, *throughout both lungs There was also a tumor* of the left lower bronchus Excisional biopsy of lung, bronchial tumor and other tissue showed lipid granulomatous lesions Honeycomb lungs may be found in association with biliary cirrhosis of infancy, pituitary disorders (diabetes insipidus) tuberous sclerosis and allied neurocutaneous disorders as well as in scleroderma Rarely is honeycomb lung due to faulty development In an instance of this type, which I reported elsewhere, there were found at autopsy multiple small cysts in both lungs associated with a patent ductus arteriosus, congenital aneurysms of the pulmonary arteries and anomalous coronary arteries

It may be mentioned at this juncture, that diabetes insipidus may be found not only in association with the histiocytoses but also in the presence of sarcoidosis various infections trauma, tumors and other conditions On rare occasion as in a case reported by Freud diabetes insipidus is associated with interstitial pulmonary fibrosis The problem arises whether the finding of the latter, in the absence of stigmata of a past or present disseminated disease, may not represent a 'forme fruste' of a more widespread occult disturbance This possibility is mentioned on several occasions in these pages, not only under the circumstances mentioned but also when indeterminate, diffuse fibrosis of the lungs occurs in the absence of any other demonstrable disease A case in point will be cited shortly which prompts such a speculation (Case 6)

Histiocytosis is probably the most frequent systemic disease associated with honeycomb lungs, especially in children MacDonald and Shanks described seven cases of honeycomb lungs in children The authors considered "xanthomatosis as the most likely cause I have encountered cystic lungs as a late event in chronic, diffuse, interstitial pulmonary fibrosis of indeterminate etiology (*see* Chapter 6) It shoul be noted however, that the examination of tissue may not reveal characteristic histiocytic cel unless the sections are properly prepared Th presupposes that the examiner is aware of or sus pects the possible presence of a histiocytic disease

allow the escape of air into the interstitial strom and subpleurally Rupture of a pleural bleb give rise to spontaneous pneumothorax which may be recurrent Long standing pulmonary disease associated with hypertension of the lesser circulation may give rise to chronic cor pulmonale, another frequent complication These several features are combined in the following patient whose course I followed for a number of years Unfortunately, the nature of the underlying disease could not be ascertained even after the examination of the lungs at autopsy, which was limited to the chest This case is included here primarily as an excellent example of honeycomb lungs The pathologist suspected a congenital cystic lung although the clinical course of the disease appeared to be more in keeping with an acquired disease

Case 6 Male—Age 37

A white male became ill on September 11, 1940 when he suddenly developed pain in the chest, lost his breath and couldn t walk The patient was hospitalized and a bilateral spontaneous pneumothorax was found with a small pneumothorax on the right side and a 50 per cent collapse of the left lung The pneumothorax gradually disappeared from both pleural cavities but the patient continued to have difficulty in breathing although not to a disabling degree He had occasional respiratory infections with cough and expectoration

Early in 1947 he had a respiratory infection At this time examination revealed evidence of clubbing of the fingers, moderate cyanosis and dyspnea on exertion Chest x rays revealed innumerable, minute cystic changes throughout both lungs from apex to base It gave the lungs a fine honeycomb appearance brought out best in tomograms (Figures 8A and B) Various laboratory tests including a survey of the skeletal system revealed no abnormal findings In the course of the following two years the patient developed increasing

dyspnea orthopnea enlargement of the liver swelling of the feet and venous engorgement indicative of right heart failure of which he died

Autopsy revealed the lungs voluminous with moderate fibrous thickening of the pleura The cut section presented an extremely interesting appearance It was sponge like due to the presence of innumerable cystic structures varying in size from several mm to 3 to 4 cm in greatest diameter The walls of the cysts were thin measuring less than 1 cm in thickness They were apparently empty and had a smooth glistening lining None appeared to be infected Occasional cysts revealed ill defined intramural yellow or pink patches The larger cysts were mostly in the upper lobe (Figure 8C) The relatively uninvolved parenchyma presented a spongy architecture due to compensatory emphysema The bronchi revealed the mucosal lining smooth pink in color no evidence of dilatation, and distinct bronchial communications could not be demonstrated The pulmonary arteries were slightly to moderately dilated but thin walled

Microscopic examination revealed the lung parenchyma for the most part replaced and distorted by cystic structures of varying size many of which were multiloculated (Figure 8D) The cysts communicated freely with one another The walls were formed by cellular connective fibrous tissue In other areas the walls were composed of dense collapsed or almost hyalinized connective tissue In some areas strands and bundles of smooth muscle fibers were present The lining of the cysts varied from tall cylindrical ciliary epithelium to cuboidal epithelium to a single layer of flat epithelium and in many areas there was no epithelial lining at all At some points the cystic structures were lined by a stratified layer composed of rather small indifferent epithelial cells which superficially but not actually resembled stratified squamous mucosa A few of the cystic structures contained material composed of degenerated macrophages edema fluid and a few polymorphonuclear leukocytes Most of them however were empty and apparently well aerated One section disclosed a free communication between a bronchiole and one of the cystic structures The cysts were empty of fluid and well aerated In a few areas small scattered collections of lymphocytes were seen adjacent to cystic structures but no significant degree of inflammation The bronchi were unremarkable and revealed no evidence of bronchiectasis A striking feature seen in all the sections was a moderate to marked degree of intimal thickening of small pulmonary arteries and arterioles The larger pulmonary arteries revealed only slight arteriosclerosis Fat stains disclosed a few scattered pseudophilic deposits in some of the denser fibrous areas

Amyloidosis of the Lungs

Amyloidosis is a disease caused by a disturbance of protein metabolism Amyloid is a translucent and structureless substance which can be distinguished by its affinity for iodine Congo red and other metachromatic dyes In spite of considerable overlapping four varieties of amyloidosis are recognized clinically according to the classification proposed by Reimann Koucky and Eklund (1) A primary atypical type (2) A much more common secondary type in association with preexisting tuberculosis bronchiectasis empyema osteomyelitis draining sinuses and other suppurative diseases (3) A type simulating the primary form but found in association with multiple myeloma and (4) A type characterized by localized deposits of amyloid causing tumor formation This type is found chiefly in the respiratory tract especially the larynx but also the heart skin and other sites

Reimann and co workers believe that primary and secondary amyloidosis have much in common Mesenchymal tissue and parenchymatous organs are affected in both and both may be systematized In their opinion the primary form is distinguished chiefly by the absence of a discernible cause by the predominant involvement of →

Figure 8 Case 6 Honeycomb lungs A (*Upper left*) Diffuse reticulations of both lungs B (*Upper right*) Tomogram showing detail C (*Lower left*) Lung Innumerable cysts more conspicuous in the upper lobe D (*Lower right*) Lung Diffuse interalveolar fibrosis many small cysts (Death due to chronic cor pulmonale)

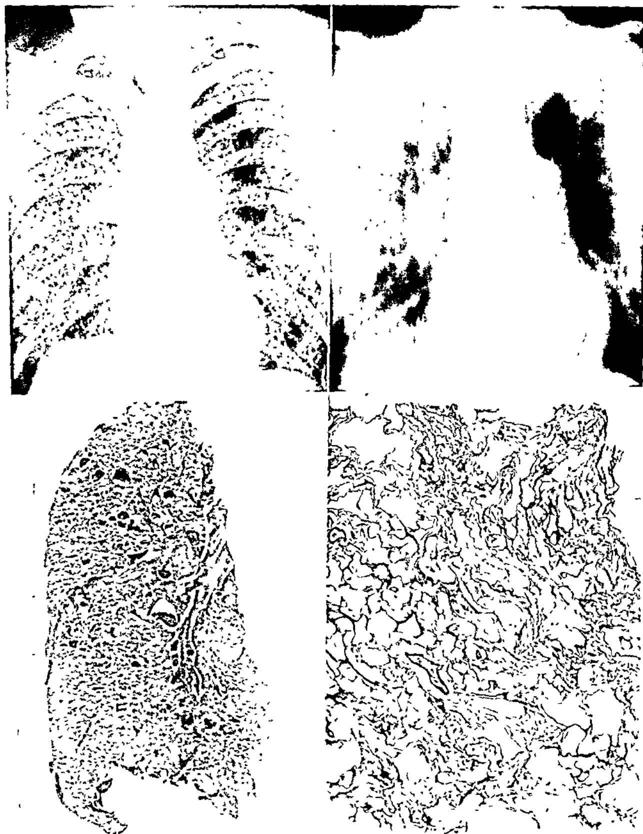


Figure 8 *(See legend on preceding page)*

the heart gastrointestinal tract lung and muscle and by its slow progression Secondary amyloidosis is characterized by a more rapid development and a predominant localization in the spleen liver and kidneys The authors believe that amyloidosis a form of proteinosis has certain features in common with other retention or storage diseases such as glycogenosis and lipidosis

The primary or atypical form of amyloidosis was first brought to the attention of physicians by Lubarch in 1929 He described three cases in two of which the lungs were involved In 1935 Perla and Gross reported three additional cases from the Montefiore Hospital New York One a female of fifty three died with signs of congestive heart failure An underlying carcinoma of the lung was suspected At autopsy the left lung showed extensive atelectasis involving the entire lower lobe and the lower part of the upper lobe A positive test for amyloid was obtained with Lugol s solution Microscopic examination revealed a peculiar homogeneous material in the walls of many of the blood vessels and the presence of amyloid material in the alveolar walls confirmed by Congo red test In addition the patient had macroglossia due to amyloidosis of the tongue and amyloid infiltration of the heart colon diaphragm and uterus A recent review on primary systemic amyloidosis by Mathews refers to ninety eight reported cases In thirty five the lungs were involved

In most instances atypical amyloidosis involves the larynx trachea or main bronchi in a few the lung parenchyma Whitwell reported the case of a forty eight year old man in whom the diagnosis was made from bronchoscopic study The author reviewed pertinent findings of ten additional cases of amyloid tumors of the lower respiratory tract reported in the literature Since the disease is found chiefly in elderly men the condition has to be differentiated from bronchial carcinoma Weissmann Clagett and McDonald found reports of three cases of localized amyloid disease of the lung and added a fourth case of their own The particular case was treated by pneumonectomy The operation was performed in an attempt to establish the cause of repeated episodes of hemoptysis The disease was found to involve the right main bronchus its branches and the corresponding branches of the pulmonary vessels and the root of the lung Later in the same year another patient was referred to the same institution for treatment of a tumor of the right lung Bronchoscopic examination did not disclose a tumor mass in the bronchus At operation the mass had all the characteristics of a malignant lesion therefore the right lung was resected Pathological examination revealed amyloid material forming a single tumor and causing obliteration of a bronchus of the right lung and collapse of the adjacent pulmonary tissue

Primary amyloidosis affects the lungs either as a diffuse interstitial fibrosis spreading from the hili into both organs or as a localized process involving one or both major bronchi simulating neoplasm The latter picture was encountered in the case reported by Perla and Gross previously mentioned as well as in the following case recently reported by Schottenfeld and co workers from the same institution

Case 7 Male—Age 43

Five years prior to admission to the Montefiore Hospital the patient noted weakness and shortness of breath Later he developed cough and expectoration On one occasion he was treated for pneumonia of the left lower lobe The symptoms of dyspnea wheezing and productive cough recurred and he was once again hospitalized for suspected pneumonia this time of the right lower lobe The patient had two additional episodes of pneumonia characterized by fever chills cough dyspnea and repeated hemoptysis prior to his present hospitalization

On admission to the hospital the pertinent findings were limited to the lungs The chest x ray revealed a large irregular density extending from the left hilar region into the left middle and lower lung fields involving chiefly the lingula (Figures 9A and B) Bronchoscopy disclosed a lesion consisting of projecting masses extending in irregular fashion from the subglottic area down to the carina which was considerably broadened and further into both main bronchi The bronchoscopist s original impression was an infiltrating carcinoma However on histologic examination no tumor was found but amyloid deposits were noted in the submucosa of the trachea (Figures 9C and D) Further studies



Figure 9 (*See legend on opposite page*)

failed to disclose any evidence of generalized amyloid disease Bence Jones proteinuria was absent, bone marrow studies were negative for myeloma

During the following year the patient had twelve additional bronchoscopic treatments to remove obstructing masses At first these were done weekly, later, at longer intervals Microscopic examinations of many sections revealed amyloid deposition in the mucosal and submucosal portions of the wall Following each bronchoscopic removal of tissue there were subjective and objective improvement After 10 bronchoscopic treatments the patient could perform a day s work comfortably but he continued to have cough and bloody sputum At the time the case was reported by the authors the patient had shown steady improvement and the chest x rays had revealed a significant decrease in size of the pulmonary density The patient went to a health resort where, after one bronchoscopic removal of amyloid tissue in a physician s office the patient began to bleed and shortly thereafter died

Metastatic Calcification of the Lungs

Introduction

This condition refers to a metabolic disorder in which lime salts are deposited in presumably normal tissues Dystrophic calcification refers to a disturbance in which lime salts impregnate tissues previously the seat of tuberculosis histoplasmosis, suppuration and other chronic diseases A clear distinction between the two forms of calcification is not always possible since combinations have been found in some cases Metastatic calcification affects most often the lungs kidneys and stomach because the normal excretion of acid from these organs is associated with greater alkalinity of the tissue cells The lowered concentration of hydrogen ions in the latter favors the precipitation of calcium and phosphorus from the serum A similar mechanism is ascribed to the dystrophic form the necrotic tissue is associated with increased alkalinity because of the lowered CO tension thus favoring precipitation of calcium phosphate

Etiology

The phenomenon of metastatic calcification has been known for a century Virchow having described the condition as early as 1855 Except for isolated case reports chiefly in journals devoted to the basic sciences little interest was paid to the disturbance until Mulligan in 1947 made an exhaustive review of all previously reported cases In recent years increasing numbers of reports have been appearing in clinical journals describing the condition in association with the following

Chronic renal disease may be associated with sufficient destruction of kidney tissue to interfere with the excretion of phosphates The accumulation of phosphate in the blood causes a temporary decrease in calcium which in turn provokes a compensatory hyperplasia of the parathyroids (secondary hyperparathyroidism) The resulting increased secretion of parathormone is soon followed by supersaturation of the serum with calcium and phosphorus ions, demineralization of the bone and the deposition of excess calcium in soft tissues In the presence of chronic glomerulonephritis associated with a marked degree of nephrocalcinosis, the calcium deposits in the kidney may, on rare occasion, be visible in roentgenograms Arons and co workers draw attention to the fact that the calcium deposition in cases of chronic glomerulonephritis associated with nephrocalcinosis, is more marked in the renal cortex in contrast to other forms of calcification (vitamin D intoxication sarcoidosis hyperparathyroidism) in which the calcification is more marked in the medullary pyramids

Primary hyperparathyroidism may cause met

Figure 9 Case 7 Amyloidosis of bronchus A (*Upper left*) Irregular density in left lower lung field increased hilar and bronchovascular marking ... mainly at the hilum and in lingula ... tunica propria (mucosa on top) ... hyaline amyloid in tunica propria ... loid masses followed by relief sy...

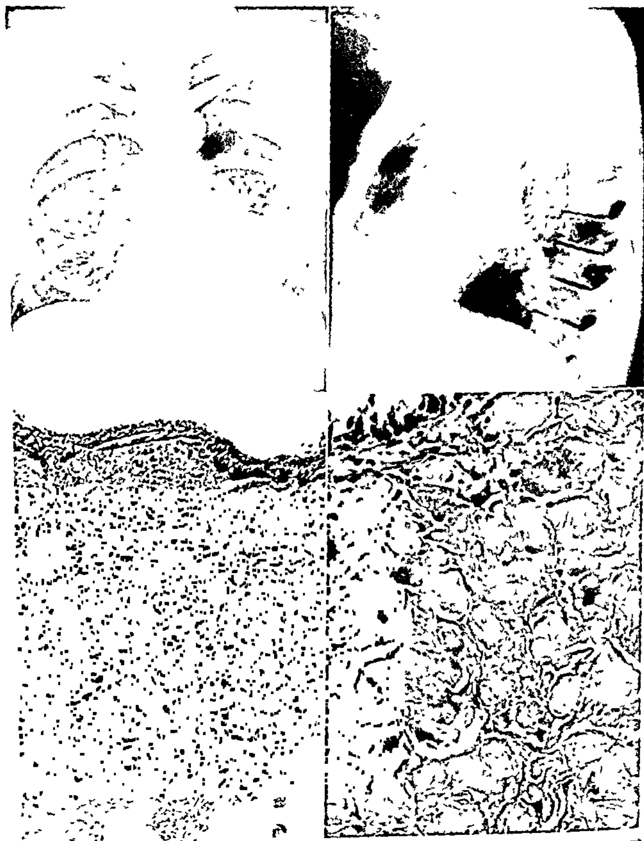


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Figure 9 *Case* 7 Amyloidosis of bronchus A (*Upper left*) Irregular density in left lower lung field increased hilar and bronchovascular markings in right lung B (*Upper right*) Lateral projection shows density situated mainly at the hilum and in lingula C (*Lower left*) Bronchus Biopsy shows amyloid deposition through entire tunica propria (mucosa on top) bronchial gland (upper left corner) D (*Lower right*) Amorphous acellular hyaline amyloid in tunica propria (mucosa at upper left) (Repeated bronchoscopic removal of obstructing amyloid masses followed by relief symptoms Exsanguinating hemoptysis) (From Schottenfeld Arnold Gruhn and Etess *Am J Med* 11 770 1951)

astatic calcification One is usually dealing with parathyroid neoplasms Usually renal insufficiency is also present so that it may be difficult to distinguish the primary from the secondary varieties Primary hyperparathyroidism is featured, in addition, by osteitis fibrosa cystica, localized giant cell tumors in the jaw and other bones and thyroid disturbances Significant laboratory findings are an elevation of serum calcium, decrease in inorganic serum phosphorus and an increase in urinary output of calcium However, the values may be within normal limits

/ *Sarcoidosis* may be associated with metastatic calcification, nephrocalcinosis, nephrolithiasis and hypercalcemia Davidson and co-workers reported seven cases of sarcoidosis with nephrocalcinosis The calcifications occurred in the sarcoid lesions but for the most part were metastatic *in nature* since they were also found in other soft tissues including the lung in one case In the particular instance, small discrete nodules of calcification were present in alveolar walls, some of which were thought to be within Schaumann bodies while others as linear metastatic calcifications In another case, the question arose as to whether or not the pulmonary changes were actually those of a miliary calcinosis A similar case was reported by Schupbach and Wernly

Davidson and co workers found that hyperparathyroidism is a disease with which renal sarcoid is most likely to be confused The differential diagnosis presented itself in two cases of a total of seven Salmon and Meynell also described a case of hyperparathyroidism simulating sarcoidosis Interestingly enough, the chest x-ray in their case showed coarse, diffuse striations in keeping with pulmonary sarcoidosis After removal of the parathyroid adenoma, the lungs showed radiographic clearing Other features in the differential diagnosis of sarcoidosis and hyperparathyroidism from a clinical standpoint are discussed in Chapter 9

/ *Destructive bone diseases*, such as primary or metastatic sarcoma, metastatic carcinoma, multiple myeloma and osteomyelitis may be associated with metastatic calcification Metastatic calcification may be present not only when there is obvious skeletal destruction but also in slow-growing carcinomas of the breast, ovary and testicles *without apparent bone involvement* (Figure 10)

/*Excessive and prolonged use of highly potent vitamin D preparations* (fortified cod liver oil or *ultraviolet* irradiated ergosterol, marketed under *various trade names) is* probably the most frequent cause of metastatic calcification Wilson *and co workers* refer to approximately 120 *reported cases of this* condition Undoubtedly a greater number have *not* been *reported In a* study of fifty six cases of vitamin D *intoxication* from a single institution, Holman found eight in which pathologic calcification occurred In addition to a history of prolonged *ingestion of massive* doses of high potency vitamin D *preparations*, there were clinical and laboratory evidence of renal insufficiency, an abnormally high concentration of phosphorus in the blood as well as the presence of rheumatoid or gouty arthritis

Prolonged and excessive intake of absorbable alkali and milk may cause hypercalcemia and metastatic calcification without renal insufficiency In the vast majority of cases the hypercalcemia is associated with renal insufficiency and azotemia In a collected series of twenty-one cases, including three of his own, Kessler found that the patients had ingested both milk and absorbable alkali, in the exception only absorbable alkali In spite of withdrawal of absorbable alkali and low calcium diet the treatment had no bearing on the outcome although improved renal function was obtained in many

Pathology

As mentioned, the lungs are among the most frequent organs involved in metastatic calcification In Mulligan's collected series, the lungs were affected in thirty of thirty-five cases with bone disease, in twelve of twenty three cases with chronic renal disease (renal rickets), in twelve of twenty-one cases with primary parathyroid neoplasms and in three of nine cases with hypervitaminosis D

Gross examination of lungs, which are the seat of metastatic calcification, may give little visible evidence of the extent of changes present within the organs even when disease is evident in other

parts of the body The lungs may have a 'normal' appearance or show only moderate emphysema In the presence of long standing disease, the organs are usually firm, tough and gritty with a network of linear streaks outlining the alveolar septa The histologic appearance of the lung as seen in a number of cases studied at the Montefiore Hospital, is characterized by the presence of minute calcific foci in the form of plates and rods impregnating the alveolar septa, also spicules of calcium, often with giant cell formation, in the interstitial fibrous tissue Calcification is seen in the walls of many of the capillaries small blood vessels, also in the capillaries of bronchioles and in the bronchi themselves In calcifying metastatic carcinoma, calcified masses impregnate the neoplastic deposits

Roentgenology

In spite of the high incidence of pulmonary involvement, metastatic calcification of the lungs is rarely recognized during life except in instances of calcifying, malignant neoplasms with pulmonary metastases In one of the cases, reported by Burnett and co workers, the calcification was sufficiently prominent to outline the bronchi in the chest x-ray The systemic nature of the disease is evident in the demineralization of long bones, diffuse calcinosis in soft tissues, especially around rheumatoid joints, and the calcified masses demonstrable roentgenologically in the abdomen, in the region of the kidneys

The failure to recognize metastatic calcification of the lungs during life is due in part to the widely scattered calcific foci in the finer architecture of the parenchyma Yet, this is probably not the major cause since similarly dispersed calcific foci are readily discernible in tuberculosis, histoplasmosis and other diseases The difficulty of diagnosis of lung lesions probably lies in the fact that metastatic calcification is usually diagnosed in the late stages of its development and any abnormal markings in the chest x rays are apt to be ascribed to associated cardiorenal compli



Figure 10 Calcifying carcinoma of breast with calcific metastatic deposits in lungs and lymph nodes A (*Left*) Calcific foci in left upper lobe and left supraclavicular lymph nodes several foci faintly seen in right upper lobe and above right clavicle fracture of second left rib, anteriorly upward displacement of left leaf of diaphragm (due to phrenic nerve involvement) B (*Right*) Lung detail (Seven years previously patient had a left radical mastectomy for carcinoma histologic examination of tumor revealed calcifying carcinoma, biopsy of supraclavicular lymph node also showed calcifying carcinoma)

cations which almost invariably coexist But if one inspects overexposed chest films or Bucky films of patients with metastatic calcification, one may be able to delineate within the visible lung fields a reticular, granular network of infiltrations or possibly calcific plaques in bronchi in keeping with the underlying disease

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Chapter 4

Diseases of the Blood

Introduction

Diseases of the blood and blood forming organs seldom affect the lungs Occasionally, sickle cell anemia and hemosiderosis rarely polycythemia vera and hemorrhagic dyscrasias are associated with pulmonary lesions The leukemias often involve the intrathoracic lymph nodes but not the lung parenchyma to an extent that the disease is demonstrable roentgenologically Infectious mononucleosis although featured by hematological findings is not strictly speaking a blood disorder being most likely caused by a virus The disease will be included in this chapter simply to round out the discussion of the subject Pernicious anemia does not involve the lungs directly but it does exert a deleterious effect on any superimposed bacterial or viral infection The frequent association of secondary anemia and diaphragmatic hernia is well recognized and need only be mentioned The loss of blood in this condition is not necessarily related to the amount of gastrointestinal bleeding

Pulmonary Diseases Associated with Unusual Blood Findings

Before elaborating on the pulmonary manifestations of blood diseases it is not out of order to discuss the reverse of the picture pulmonary diseases which may be associated with unusual blood findings

Tuberculosis

The simultaneous occurrence of leukemia and tuberculosis has been noted on many occasions The presence of one disease need not influence the course of the other At times a dormant tuberculosis may become activated by a superimposed leukemia or else an existing leukemia may become suppressed with the appearance of active tuberculosis In many cases it is difficult to establish an exact chronological let alone causal relationship between one disease and the other Some of the older writers speculated that tuberculosis may be a cause of leukemia The majority nowadays believe that the blood changes are of leukemoid nature rather than a true leukemia Difficulties in differential diagnosis often arise when a leukemoid blood picture is present but a definition of the latter may not be easy Hill and Duncan consider as leukemoid any reactions in which the following are found (a) a total leukocyte count over 50 000 (b) the presence of immature cells of the blast type or (c) a combination of (a) and (b) A third prerequisite offered by Heck and Hall, is that at autopsy the organs and tissues should show no leukemic changes

Leukemoid reactions of the granulocytic (myeloid) type are encountered in acute generalized hematogenous tuberculosis Leibowitz reported the case of a twenty nine year old white female who had evidence of tuberculosis of both upper lobes and spine and who developed an acute activation of the disease featured by a myeloblastic blood picture Because of the severity of the illness profound anemia lesions of the mouth purpuric spots high fever and hepatosplenomegaly the diagnosis was that of an acute myelogenous leukemia until the postmortem examination revealed that the patient had died of a tuberculous septicemia with widespread caseo-

necrotic foci containing masses of acid fast organisms Leibowitz refers to several cases reported by others in which acute forms of hematogenous tuberculosis were associated with bizarre blood pictures

A case was recently discussed at a clinicopathological conference by Kuzma and others in which a sixty four year old patient developed symptoms and signs in keeping with a right lower lobe pneumonia The hematological findings were featured by anemia leucopenia and thrombocytopenia The patient died and at autopsy the liver spleen kidney and lymph nodes showed caseous tuberculous abscesses containing large numbers of tubercle bacilli The lesions were of a soft variety with very little tissue reaction in the way of giant cells fibrosis or lymphocytosis Hendry found that tuberculosis when associated with thrombocytopenia is almost invariably a disseminated disease In such cases it is presumed that the bone marrow involvement is the factor responsible for the onset of the purpura In a small number tuberculosis causes thrombocytopenic purpura When thrombocytopenic purpura occurs in other forms of tuberculosis the association is merely coincidental

From an experience with a sizable number of patients with generalized hematogenous tuberculosis I am impressed with the much more frequent occurrence of an absolute or relative leucopenia and a relatively high lymphocytic count rather than a leukomoid picture Leucopenia is apt to be encountered in hematogenous tuberculosis affecting the abdominal organs especially the spleen The abdominal distress vomiting fever and prostration a relatively low pulse leucopenia an enlarged spleen even a rash in the skin characterize the so called typhoid form of hematogenous tuberculosis (Landouzy)

On rare occasion tuberculosis may be associated with polycythemia This combination is more apt to occur in patients with chronic recrudescent hematogenous tuberculosis in which the spleen is the major seat of involvement I have met with two patients in whom the presence of an enlarged spleen led to a mistaken diagnosis of Banti s disease Cases are also on record of acute generalized hematogenous as well as chronic caseocavernous tuberculosis occurring in association with polycythemia But it is not always easy to determine whether or not one is dealing with polycythemia vera or polycythemia occurring in response to increased oxygen demand On rare occasion as pointed out by Fountain generalized hematogenous tuberculosis may be associated with profound depression of hematopoieses resulting in pancytopenia and a picture in keeping with aplastic anemia

MALIGNANT NEOPLASMS

Leukemoid reactions may be encountered in association with malignant neoplasms including those of the lungs As a rule the malignancy is in an advanced stage and skeletal metastases are present Fahey reported leukemoid reactions in three of 160 cases of carcinoma of the lung Similar experiences have been cited by others In a case reported by Henkin bone metastases became visible roentgenologically five months after the height of the leukemoid reaction In a patient recently examined at autopsy at Montefiore Hospital there was found a bronchiogenic carcinoma with widespread bone and visceral metastases There was a coexisting chronic lymphocytic (lymphatic) leukemia (WBC 56 000 to 101 000 lymphocytes 90 per cent) affecting the bone marrow spleen and liver The symptoms referable to the pulmonary disease and the recognition of the leukemia occurred within one month of each other

Among the various causes of eosinophilia malignancy is also occasionally mentioned Isaacson and Rapoport described fifteen cases of eosinophilia in a review of 2 363 cases of malignancy The authors found nineteen additional cases reported in the literature including two instances of bronchiogenic carcinoma with widespread metastases Attention is drawn to the fact that in 90 per cent of the cases metastases were present and that in an additional 7 per cent metastases were suspected but not proved In the instance of bronchiogenic carcinoma described by these authors the metastases were so widespread and the leukemoid reaction and eosinophilia so pronounced that a diagnosis of eosinophilic leukemia was made clinically

Malignant pulmonary neoplasms may also be complicated by hemolytic anemia. The type of anemia encountered has been designated by Singer and Dameshek as the symptomatic hemolytic variety. A rare instance of a large anterior mediastinal tumor complicated by aplastic anemia is reported by Humphreys and Southworth. A woman, aged fifty eight, had been treated for almost two years with repeated blood transfusions without effect. After removal of the tumor, which histologically appeared to be probably thymic in origin, there was a sharp rise in reticulocytosis and the erythrocyte count returned to normal range. The patient died one year after the operation. Autopsy revealed many deposits of iron pigment in the tissues. It was suspected that death was caused by liver insufficiency secondary to advanced hemochromatosis due to the long course of transfusions. The authors refer to another instance, reported by Opsahl, of thymic carcinoma complicated by aplastic anemia.

Although not directly bearing on the subject it might be interesting to mention a case recently observed at the Montefiore Hospital. A fifty-year old woman had been suspected of having miliary tuberculosis. The illness had lasted about four months, the symptoms and signs for a time pointed to a viral infection. The initial chest x ray was negative but subsequent x rays revealed increasing crops of miliary foci seeding both lungs. The patient developed ecchymoses over the thighs. A blood examination by Dr. S. Melamed revealed a thrombocytopenia of an aplastic variety (platelet counts ranged from 50,000 to 75,000). In spite of repeated blood transfusions the patient died. The autopsy revealed a primary adenocarcinoma of the ascending colon and widespread metastases to the lungs, lymph nodes, dura and bones. Cone and Nayer reported a case of thrombocytopenic purpura complicating primary bronchiogenic carcinoma. The blood findings indicated metastatic involvement.

Sickle Cell Anemia

In 1910 Herrick described a case of severe anemia characterized by peculiar elongated sickle shaped red blood corpuscles. Since the publication of this report, sickle cell anemia has become recognized as a primary, hereditary, blood dyscrasia affecting Negroes almost exclusively. It is estimated that the sickle cell trait (sicklemia), in the absence of the specific hemolytic anemia, occurs in from 7 to 8 per cent of Negroes in the United States. The ratio of sickle cell anemia to the sickle cell trait is about one to forty. In acute sickle cell anemia the elongated multipointed erythrocytes interlock and obstruct the capillaries, the resulting stagnation of blood causing congestion, thrombosis and infarction of the affected parts. The accompanying destruction of erythrocytes gives rise to varying degrees of hemolytic anemia. Although the major pathological changes are found in the bone marrow, skeletal system and spleen the disease may affect any organ. The most pronounced symptoms are associated with, so-called, sickle cell crises which recur from time to time and are characterized by fever and pain in the abdomen, thorax and joints. Additional signs are jaundice, lymphadenopathy, cardiac enlargement, ulcers of extremities, hemorrhagic tendencies and respiratory infections.

The pulmonary manifestations of sickle cell anemia have received comparatively little study although respiratory tract infections are common, often precipitating crises and frequently causing death. In a study of fifty four cases of sickle cell anemia, Henderson found pneumonia a presenting sign in fourteen. In a similar study of thirty-seven children, Scott and co workers found twelve with roentgen evidence of pulmonary congestion or consolidation. In a review of seventeen consecutive cases of sickle cell anemia treated at the Morrisania City Hospital, I found only three instances in which the chest x rays failed to reveal some type of abnormality. Many of the patients had been hospitalized repeatedly during recurring crises or for treatment of intercurrent complications. Pregnancy is a particularly serious hazard to the mother as well as to the fetus.

The pathological changes in the lungs are characterized by capillary stasis, a tendency to thrombus formation and infarction. Roentgeno-

logically one meets with a variegated picture, a normal chest x ray being seldom seen There is a constant lability in the roentgen changes Marked variations are noted in the size and configuration of the cardiac silhouette The pulmonary markings range the gamut from increased bronchovascular shadows to irregular patchy infiltrations in the mid and lower portions of the lungs or massive consolidations After frequent transfusions one may encounter a soft veil like haziness over both lung fields On rare occasion one finds nodular densities symmetrically distributed in both lungs in keeping with hemosiderosis or minute infarctions The evanescent nature of the roentgen changes usually preclude exact definition of the nature of the pulmonary lesions In many instances the findings are in keeping with pulmonary congestive changes possibly associated with pulmonary infarction

Case 8 Female Negro—Age 31

Admitted to the obstetrical service of the Morrisania City Hospital on July 27 1949 in acute respiratory distress and generalized edema which had been getting progressively worse during the preceding week During the twenty four hours prior to her admission to the hospital the patient had not felt fetal movement The patient had made one prenatal visit three months previously and subsequently had attended the cardiac clinic for suspected heart disease The patient had three normal spontaneous deliveries in 1937 1939 and 1947 In 1940 she had a stillborn breech delivery Following that delivery she had a seizure of respiratory distress and was given a blood transfusion Since childhood the patient had joint pains and unexplained anemia which were ascribed to rheumatic fever

Physical examination revealed a critically ill woman markedly dyspneic and orthopneic The fetal heart sounds were not heard There was moderate edema of the abdominal wall and marked edema of the lower extremities The hemoglobin was 1 5 gms red blood cells 580 000 white blood cells 31 000 The reticulocyte count was 16 per cent The urine showed 3 plus albumin and was positive for bile and urobilogen. External marrow smears showed a hyperactive bone marrow A sickle cell preparation at 10 hours showed 95 per cent sickling The patient was placed under oxygen and given repeated blood transfusions She soon began to complain of severe abdominal pain for which she received sedatives and demoral Two days after admission she had a chill progressive rise in temperature and the patient was started on penicillin A chest x ray at this time revealed diffuse infiltrations in both lungs with an irregular triangular area of density in the right midlung field with accentuation of the small fissure also obscuration of both costophrenic sinuses The cardiac shadow was enlarged and the pulmonary conus prominent Both leaves of the diaphragm were displaced upward (Figure 11A)

The following day the patient went into spontaneous labor and after one hour delivered a seven pounds 7 ounces stillborn macerated infant The uterus contracted well and there was a normal amount of blood loss Immediately after delivery the temperature rose to 103 4° the hemoglobin was 8 gms Blood transfusions were continued On the third day postpartum the temperature returned to normal The blood picture showed progressive improvement and the patient was discharged to the clinic on the tenth postpartum day A late follow up chest x ray showed almost complete disappearance of the infiltrations in both l ng ...

As might be expected tuberculosis is another serious complication frequently encountered in patients with sickle cell anemia Weiss and Waife found that Negroes with sickle cell anemia show a higher incidence of pleuropulmonary inflammatory disease as evidenced by a higher incidence of pleural adhesions and a higher incidence of various forms of tuberculosis than do Negroes without sickle cell anemia Weiss and Stecher also found that the sickling trait is more than twice as common (12 6 per cent) among tuberculous Negroes admitted to the Philadelphia General Hospital as among non tuberculous Negroes admitted to the same hospital (5 3 per cent) In their study, exudative tuberculosis was found twice as common among tuberculous Negroes with the sickling trait (74 per cent) as among tuberculous Negroes without the trait (38 per cent) The authors concluded that the sickling trait has a definite clinical significance and is a factor in the response of some Negroes to tuberculous infection The findings of Weiss and co workers have not been confirmed by



Figure 11 *Case 8* Sickle cell anemia with pulmonary invol
gestive changes in both lungs especially the midportions and
bases heart enlarged diaphragm displ upward *B* (*L*
filtrations accentuated hilar markin nlarged hea
zure in a woman with anemia co

A (*Upper*) Marked con
areas of consolidation at
s derable clearing of in
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Rosenblum and co workers who found that neither the extent of the pulmonary tuberculosis nor the age at which it first became clinically evident was influenced by the coexistence of the sickle cell trait

It might be interesting to cite an experience with a Negro girl with sickle cell anemia who was under my observation for a number of years and who presented an unusual course of events The patient was first admitted to the Morrisania City Hospital at the age of fourteen with advanced caseocavernous tuberculosis of the left upper lobe She had been treated previously at the hospital on various occasions for recurrent sickle cell crises After the diagnosis of tuberculosis was made a left sided pneumothorax was induced and the treatment continued at the Seton Hospital In time the patient developed a pleural effusion and the pneumothorax had to be abandoned When streptomycin became available she received the antibiotic for two months and eventually the disease became arrested At the age of nineteen she became pregnant and delivered a live infant This young Negro girl with sickle cell anemia was able to overcome an advanced tuberculosis and to go through pregnancy successfully accomplishments worth citing It might be pertinent to add that since the introduction of potent antibacterial agents the lives of many patients with sickle cell anemia have been materially prolonged

Pulmonary Hemosiderosis

Focal deposits of iron particles in the lungs may arise from exogenous as well as endogenous sources Exogenous siderosis may be due to inhalation of dusts or fumes in occupations in which ferrous metals are used The disease is encountered among metal grinders arc welders and silver finishers Endogenous siderosis (hemosiderosis) is a non occupational disease occurring in association with long standing mitral stenosis advanced left ventricular failure following repeated blood transfusions in certain forms of malnutrition encountered in South African Negroes and as a result of excessive parenteral administration of iron Pulmonary hemosiderosis may also occur without apparent cause The latter form is known as idiopathic hemosiderosis of the lungs

In Association with Mitral Stenosis

Until recently the association of hemosiderosis and mitral stenosis was considered a rarity as attested by the occasional reports describing single cases Lately there has been an increasing awareness of this condition as a result of more frequent chest roentgenography A valuable contribution to the subject was made by Enticknap and co workers who reported findings on lingular biopsies obtained from forty patients who had mitral valvulotomy The biopsies were done in an attempt to correlate the pathological findings with the clinical state and catheter studies of individual patients Of particular interest were the high degree of parallelism between the extent of hemosiderosis present in the histological sections and the amount of roentgenological mottling The roentgenological assessment was made according to a scale graded from 3 to 0 depending on the degree of mottling The latter was compared with a histological scale based on the density of siderophores and the total number of foci seen in the sections The authors found that hemosiderosis was almost universal in patients showing the clinical effects of mitral stenosis and that there was a reasonable correlation between the individual assessment of hemosiderosis from the roentgenological appearance and the histological findings at lingular biopsy

Analogous observations were reported by Lendrum and co workers These investigators found focal hemosiderin deposits of various degrees in every instance of twenty six cases of mitral stenosis in which abnormalities of the tricuspid valve were slight or absent These authors likewise concluded that hemosiderosis apparently occurs in every case of mitral stenosis associated with right ventricular hypertrophy The authors failed to find hemosiderosis in the absence of right ventricular hypertrophy because of an as

sociated tricuspid stenosis or other factors Taylor and Strong found focal accumulation of hemosiderin containing phagocytes forming distinct nodules in the lungs in 4? per cent of cases dying with advanced mitral stenosis In an additional 31 per cent the lungs presented the more classic finding of brown induration i e diffuse siderophages without distinct focal collections Esposito reported a somewhat lower incidence of hemosiderosis in rheumatic heart disease Of 100 patients examined at autopsy twenty eight showed histopathological changes being more pronounced in advanced disease

The *mechanism of hemosiderosis in patients* with mitral stenosis is readily understandable The engorgement of the pulmonary capillaries incident to the hypertension of the lesser circulation caused by the stenotic mitral valve gives rise to recurring minute hemorrhages in the air spaces After hemolysis of the extravasated red cells the liberated iron free fraction (hematin) is absorbed the iron containing fraction (hemosiderin) remains in the tissues and initiates a foreign body reaction The minute dark brown spots often visible grossly in the visceral pleura and readily on histological examination of the tissues consist of irregularly distributed nodules within the lung alveoli and in the adjacent stroma (Figures 12C and D) The nodules represent deposits of hemosiderin at times accompanied by fibrous proliferation of the alveoli There may be an associated giant cell reaction occasionally calcification and on rare occasion ossification However Taylor and Strong believe that the small calcified or bony nodules are distinct from and unrelated to the aggregates of siderophages which do not contain any stainable calcium They believe it more likely that the bony and calcific nodules are the end result of rheumatic pneumonia organized thrombi or other pathologic lesions Kent and associates reported a case of pulmonary microlithiasis and referred to fourteen additional cases reported in the literature This rare disease is caused by the deposition of innumerable minute intraalveolar calculi throughout the lungs The calculi resemble morphologically corpora amylacea and the condition has been described under the latter heading Noteworthy is the fact that among the agents which might be responsible mitral stenosis is mentioned by several observers

Pulmonary hemosiderosis associated with mitral stenosis manifests itself roentgenologically in fine nodular densities diffusely scattered throughout both lungs but most numerous in the midportions (Figure 12A and B) According to Lendrum and associates the concentration of nodules in the midlung regions is due to the superimposition of tiny radiopaque nodules in the traversed lung Depending on the thickness of the lung these nodules appear more numerous in the central portions and fade away toward the periphery The nodules resemble those of miliary tuberculosis welders siderosis fine nodular forms of pneumonoconiosis and histoplasmosis There is usually little interstitial reaction between individual nodules On rare occasion the nodulations are limited to a portion of a lung and the significance of such dispersions is easily overlooked unless one bears hemosiderosis in mind This applies also to instances in which the roentgenological mottling is indefinite or not easily distinguishable from normal vascular markings In any event in the presence of mitral stenosis and hypertension of the lesser circulation such mottlings are almost invariably due to hemosiderosis At one time they were erroneously ascribed to miliary lung stasis congestion of the lungs or blood vessels caught on end I have followed the course of events in a man of twenty seven who had rheumatic mitral disease since childhood The minute nodules seen initially and simulating miliary tuberculosis gave way in time to a fine interstitial striation The miliary foci were discovered in the course of a preinduction chest x ray examination During the past twelve years the patient has remained well and at work

Idiopathic Pulmonary Hemosiderosis

This condition first described by Ceelen in 1931 is encountered chiefly in infancy and childhood but at least four cases have been reported in ages ranging from sixteen to thirty eight (Tait and Corridan) In 1948 Wyllie and co workers described seven cases and summarized seventeen

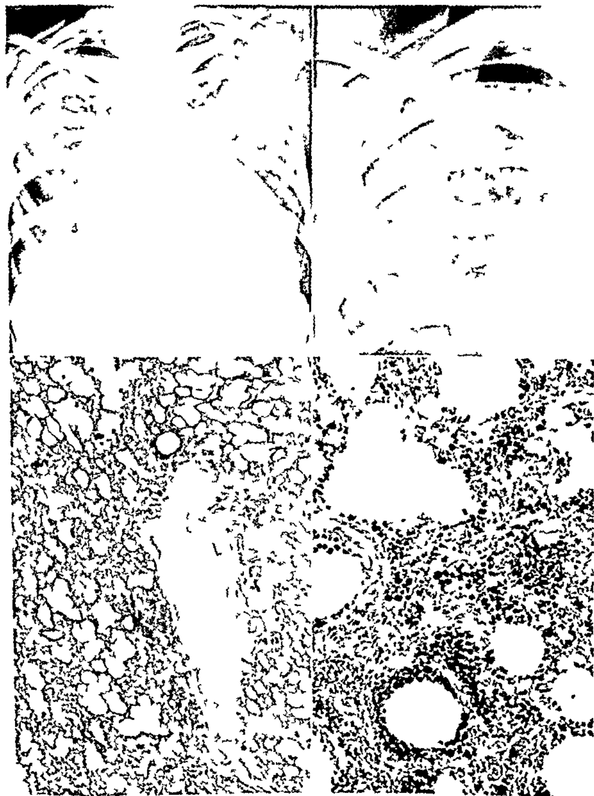


Figure 1 (See legend on next page)

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previously reported cases. Six years later Fleischner and Berenberg were able to collect thirty-one reported cases and cited an additional case of their own. Apparently the disease is being discovered more frequently in recent years. Idiopathic pulmonary hemosiderosis manifests itself by a sudden onset and recurring seizures of tachycardia, cyanosis, dyspnea, cough, hemoptysis, at times jaundice, in association with hypochromic anemia without evidence of generalized hemolytic tendency. The sputum and gastric washings may reveal iron containing macrophages. In the late stages of the disease there may be a compensatory polycythemia. There is often fever and abdominal pain. The seizures last several days and subside. With recurring episodes of increasing severity, larger portions of the lungs become involved leading eventually to a fatal outcome. The disease is not part of a generalized hemosiderosis nor is it related to hemochromatosis since there is no general disturbance of iron metabolism. The cause of the disease is unknown.

At autopsy the lungs are firm, beefy and reddish brown in color. Small hemorrhages may be seen on the pleural surface as well as within the lung substance. The changes in the lungs are characterized by diffuse interstitial fibrosis, often a necrotizing endarteritis chiefly of the small vessels and an increase in reticulum and muscle which reduce the distensibility of the lungs. The resulting blood stasis is followed by hemorrhage with deposition of iron deposits in the tissues. Microscopic examination reveals hemosiderin-laden phagocytes in the alveoli, alveolar walls and in the interalveolar tissues. The alveolar walls are thickened as is the interstitial parenchyma. Lendrum and co-workers could find no significant differences in the histologic changes of idiopathic pulmonary hemosiderosis and hemosiderosis secondary to mitral stenosis except for the more diffuse nature of the former.

The reported cases of idiopathic pulmonary hemosiderosis, summarized by Wyllie and associates, reveal no distinguishing physical features excepting for the occasional presence of clubbing of fingers and evidence of heart failure in the late stages of the disease. The disease is characterized roentgenologically by fine, diffuse, mottled infiltrations variously described as having a "smoky," "ground glass," "mossy," or "pumice stone" appearance. The involvement is bilateral and is most pronounced in the hilar regions. The fine nodules bear superficial resemblance to miliary tuberculosis but on closer inspection the changes are more in keeping with sarcoidosis or lipidosis (Wyllie *et al.*). The roentgenologic markings vary with the clinical course of the disease. Fleischner and Berenberg note that infection and atelectasis may complicate the roentgen appearance.

Hemosiderosis Due to Iron Overload

Hemosiderosis may follow repeated blood transfusions or excessive parenteral administration of iron. The condition has been observed in malnourished Africans with pellagra who subsist mainly on a diet of corn meal. It is believed that the iron may come from the utensils used in the preparation of the food. The organs chiefly involved are the Kupfer cells of the liver and the other reticuloendothelial cells of the body. The nature of the pulmonary involvement has received little study. However, one is impressed with reddish brown appearance of the lungs and the pigment laden phagocytes found in the alveolar spaces. The experimental studies of Nissen are particularly revealing. This investigator found that four hours after intravenous injections of

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Figure 12. Hemosiderosis of lungs in association with rheumatic heart disease. A (*Upper left*) Miliary infiltrations in both lungs especially mid thirds; heart greatly enlarged. B (*Upper right*) Lung detail showing miliary foci. C and D (*Lower left and right*) Microscopic sections showing focal deposits of dark staining iron pigment in perivascular and interstitial tissues. (Autopsy disclosed old rheumatic valvulitis of mitral valve with stenosis and insufficiency, dilatation and hypertrophy of left auricle, right ventricle and right auricle, chronic passive congestion and siderosis of lungs, chronic passive congestion of liver and spleen.) (From Rubin: *Diseases of the Chest*. W. B. Saunders Co.)

large doses of saccharated iron oxide iron containing leukocytes are seen in the large vessels of the lungs The lung capillaries also contain large numbers of similar cells while a few larger iron containing cells appear to be held up as capillary emboli

Womack and Brownlee found reports of twenty five cases of hemosiderosis which occurred after repeated blood transfusions From the few chest x rays available for study it appears that the roentgen changes consist of a diffuse interstitial reaction resembling that observed in the idiopathic rather than the mitral type of disease Were chest x rays taken routinely after massive or repeated blood transfusions there is reason to believe that the lungs would be found the site of siderotic deposits more often than is realized A large transfusion of blood or fluid over a relatively short period may be followed by symptoms and signs of pulmonary edema Roentgenologically one may find a veil like density obscuring both lung fields probably representing acute overload of the lesser circulation After repeated blood transfusions one may see fine stippling It is often difficult to interpret the lesions seen in chest x rays of patients with blood dyscrasias because of the difficulty of determining whether they are due to the underlying disease or the result of blood transfusions so often utilized in the treatment Even the findings at autopsy may not provide an answer Reported cases of blood dyscrasias associated with pulmonary lesions often neglect to take this factor into consideration

Case 9 Male—*Age 59*

Was well until 1945 when he developed a primary polycythemia The hemoglobin was 17 gms and the red blood cells 6 300 000 The patient was treated with irradiation Later a diagnosis of myelofibrosis was made and the patient was treated with multiple blood transfusions He soon developed a greatly enlarged spleen and liver and in time showed increasing jaundice weakness and urinary tract infections On admission to the Montefiore Hospital examination revealed a chronically ill appearing man anemic icteric with hepatosplenomegaly Blood and chemical studies also biopsy of an iliac crest confirmed the diagnosis of myelofibrosis and osteosclerosis Representative blood counts showed hemoglobin ranging from 2 2 to 5 8 gms red blood cells 0 3 to 1 9 million white blood cells 77 500 to 39,200 and abnormal differentials

The patient was initially treated with packed red cells digitalis and mercurials Because of a comparatively little increase in hemoglobin and progressive increase in the icteric index indicative of progressive hemolysis he was given transfusions of fresh blood with some improvement He also received cortisone with questionable results although he required less frequent transfusions During one period of seventy two hours during which he received three transfusions after he had had several in the preceding days a chest x ray showed diffuse small irregular infiltrations throughout both lung fields associated with dyspnea and orthopnea The picture was in keeping with pulmonary edema The patient was treated with ACTH and the transfusions were temporarily discontinued A later chest x ray showed almost complete disappearance of the infiltrations (Figures 13A and B) The patient s course was progressively downhill and he died six months later

The autopsy showed focal myelofibrosis and osteosclerosis hemosiderosis of the spleen lymph nodes liver and pancreas periportal fibrosis of the liver generalized edema of viscera generalized anasarca and serous effusions and pulmonary edema The heart was flabby dilated in all chambers with minimal hypertrophy of the left ventricle The lungs appeared brownish red with anthracotic pigment The alveolar spaces were filled with edema fluid

Although not directly related to the problem it may be appropriate to mention that transfusional hemosiderosis and hemochromatosis with which the former may be confused are distinct entities Kleckner and co workers note that transfusional hemosiderosis occurs as often in women as in men cirrhosis of the liver is lacking or is a coincidental finding and diabetes mellitus and skin pigmentation are infrequent On the other hand hemochromatosis occurs almost exclusively among men usually in later life and there is associated cirrhosis of the liver diabetes mellitus skin pigmentation and testicular atrophy The most reliable method of diagnosing hemochromatosis is by needle biopsy of the liver

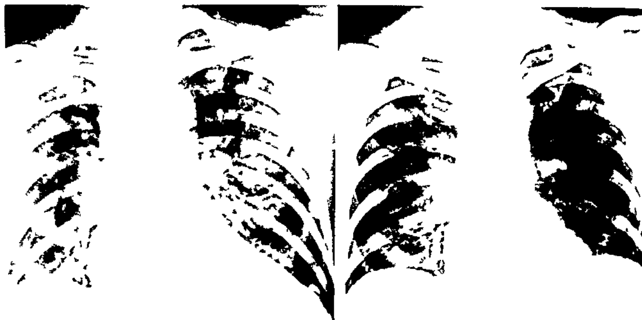


Figure 13 *Case 9* Pulmonary hemosiderosis secondary to primary polycythemia A (*Left*) Diffuse small n B (*R g/t*) and osteo

Polycythemia

Anoxia causes an increase in circulating erythrocytes to augment the oxygen carrying capacity of the blood The resulting polycythemia is a compensatory mechanism a phenomenon encountered at high altitudes in association with cavernous hemangioma of the lung congenital maldevelopments of the heart and large blood vessels and in a variety of chronic pulmonary diseases including advanced emphysema fibroid tuberculosis and pneumonoconiosis Diseases associated with pulmonary arteriosclerosis are particularly apt to be associated with polycythemia Polycythemia vera (erythremia) on the other hand is a hematologic disorder characterized by excessive erythropoiesis due to hyperplasia of the red bone marrow In addition to symptoms of anoxia polycythemia vera is featured by enlargement of the liver and spleen hyperglobulinemia an elevated metabolic rate leukocytosis and other signs pointing to a primary blood dyscrasia The differential diagnosis between the primary and secondary forms of polycythemia may be quite difficult Under such conditions the appearance of the chest x ray may be helpful

Hirsch also Hodes and Griffith note that in patients with polycythemia vera there may be present accentuation of the bronchovascular markings as well as infiltrations and discrete spherical lesions in the midzones of the lungs The prominence of the truncal shadows is due to vascular engorgement The discrete nodular lesions are believed to represent thromboses of pulmonary veins although stasis and infarction are also possibilities On the other hand, in polycythemia associated with pulmonary vascular sclerosis the middle and peripheral zones of the lungs are usually within normal limits in spite of the prominence of the right heart and pulmonary conus In a study of the chest x ray findings in thirty six patients with polycythemia vera Hodgson and co workers noted varying degrees of parenchymal involvement in twenty five The abnormalities consisted of bilateral passive congestion increased fibrosis of the bases infiltrations of both lungs and increased broncho vascular markings The findings of these authors are in agreement with those of Hodes and Griffith Although cardiac enlargement often

coexists there are a sufficient number without this complication to warrant the conclusion that the pulmonary changes are probably related the polycythemia

Hemorrhagic Diseases

Blood dyscrasias associated with an abnormal tendency to bleeding rarely affect the lungs This is somewhat surprising in view of the vulnerability to hemorrhage of other parts of the body especially the oropharynx and larynx Blood aspirated from the latter may cause respiratory distress Freedman and co workers reported one instance of hemophilia and another of thrombocytopenic purpura associated with nontraumatic hemothorax The patient with thrombocytopenic purpura died and the postmortem examination revealed hemorrhage from the intestinal mucosa perforation of the left diaphragm a sanguino purulent empyema in the left chest and necrosis of the left lower lobe of the lung

Di Cara reported a case of spontaneous hemothorax in a patient suffering from thrombocytopenic purpura and pulmonary tuberculosis The treatment of the hemothorax presented great difficulties because of the patient s allergic reactions to blood transfusions After a stormy course involving treatment with intercostal catheter drainage intrapleural instillation of streptokinase streptodornase and breathing exercises also antituberculosis drugs the patient recovered The author suspected that the cause of the spontaneous hemothorax was probably due to rupture of an adhesion or bulla involving vascular channels Di Cara cited a similar case reported by Pitt in 1900 which ended fatally and also the case of Freedman and co workers mentioned above

In a study of causes of hemorrhagic pleural effusions Berliner did not find a single instance of blood dyscrasia in 120 cases analyzed Scurvy, purpura and hemophilia as well as icterus and severe anemia are mentioned in Berliner s review as possible causes of hemorrhagic pleural effusions Pendergrass and Neuhauser described a case of interlobar hemorrhage in a patient with hemophilia The roentgen shadow simulated a parenchymal lesion Jersild reported the case of a woman aged twenty two who had Schonlein Henoch purpura The chest x ray revealed an area of infiltration in the right lung which appeared to be a well organized hematoma Following administration of vitamin P (citrin) there was complete disappearance of the symptoms On a previous occasion the same investigator, while treating a number of patients with citrin for hemorrhagic diathesis observed another woman of thirty seven who had hemoptysis and roentgen changes in the lungs The underlying condition was ascribed to avitaminosis Under treatment the tendency to hemorrhage and the lung symptoms receded

Leukemia

Leukemia is a condition in which there is proliferation of the leukoblastic cells of the body ie abnormal state usually but not invariably manifesting itself in the blood When not reflected in the blood the condition is referred to as aleukemic or subleukemic leukemia and the diagnosis is then made by study of the bone marrow Dameshek recognizes four classes of leukemia according to the predominant cell type (1) granulocytic (myelogenous) (2) lymphocytic (lymphatic) (3) monocytic and (4) plasmocytic (multiple myeloma) There are acute chronic and intermediate forms of the disease The leukemias are allied to the malignant lymphomas of which Hodgkin s disease and lymphosarcoma are the most prominent members

There is an erroneous impression that leukemic involvement of intrathoracic structures is unusual although a number of studies have shown the contrary to be the case Among forty eight cases of leukemia with typical blood pictures Kirklin and Hefke found involvement of the thorax in ten cases Of these, six were instances of chronic lymphocytic leukemia two of chronic granulocytic leukemia and two of acute leukemia Vieta



Figure 14. Acute lymphatic leukemia with intrathoracic manifestations. A (*Left*) Lobulated density at the left hilum, linear horizontal infiltrations in left lower lobe. B (*Right*) After radiotherapy, regression of hilar density, linear horizontal infiltrations persist. (Patient eventually died. Autopsy revealed acute lymphatic leukemia involving spleen, liver and bone marrow; no evidence of leukemic infiltrations in lungs.)

and Craver found roentgenologic evidence of intrathoracic involvement in 72 per cent of cases of lymphocytic leukemia, the majority revealing enlarged hilar or mediastinal lymph nodes or both. The lung parenchyma was involved in 24.6 per cent and the pleura in 12 per cent, a pleural effusion being demonstrable in 12 per cent. The incidence of intrathoracic involvement in granulocytic leukemia was found to be much less. Of fifty-two cases of the latter, discrete nodes at the lung roots were present in chest x-rays in 9.6 per cent and parenchymal infiltrations in 7.6 per cent. Bichel in a study of 217 cases of leukemia could find no definite evidence of mediastinal changes in any of the granulocytic leukemias but in the chronic lymphocytic type it was usual to find on roentgen examination some degree of hilar lymph node involvement. The high incidence of intrathoracic involvement, especially in the lymphocytic type of leukemia, is mentioned by Falconer and Leonard and others.

As is true of intrathoracic lymphomas as a group, and this applies especially to the leukemias, the physical examination of the chest gives little information. Excepting cases in which large mediastinal tumors are present, usually thymic in origin, bronchial obstructive phenomena such as wheezing respiration and sputum retention are uncommon. If the mediastinal tumor is unusually large there may be cough, seizures of dyspnea, especially in the prone position, and signs of pressure on the superior vena cava. Inasmuch as the disease is not of a directly invasive nature there is rarely evidence of involvement of the sympathetic, recurrent laryngeal or phrenic nerves. The presence of a Horner's syndrome or a paralyzed diaphragm in a patient with a mediastinal mass speaks more for carcinoma.

The roentgen manifestations of the leukemias do not differ significantly from those encountered in Hodgkin's disease or lymphosarcoma, excepting for the possibly larger tumefactions encountered in the latter. The most frequent findings are enlarged hilar lymph nodes with little if any evidence of extension of the process into the adjoining lung tissue (Figures 14A and B). If the latter is grossly involved, the permeation is along peribronchial and perivascular channels. Isolated pulmonary infiltrations are seldom recognized roentgenologically although often seen on histological examination of tissues (Figures 15A and B). Joachim and Loewe reported a unique case of granulocytic leukemia featured roentgenologically by patchy migratory infiltrations in both lungs. These were believed to be either embolic or infarctive in nature. The findings at

autopsy were in keeping with repeated infarctions secondary to vascular occlusions

Nathan and Sanders studied fifty-nine autopsied cases of acute leukemia They noted that hilar lymph node involvement and pleural effusion were frequent but gross lung involvement is rare However, on microscopic examination they found fourteen or 23 7 per cent to have definite leukemic involvement of the pulmonary parenchyma, chiefly in the walls of the alveolar septums near small bronchioles and blood vessels and subpleurally Except for the occasional presence of a pleural effusion, the chest x rays are usually negative insofar as pulmonary lesions are concerned

Myeloma

This disease occupies a position somewhere between frank tumors and leukemias The growths, usually arising in bone marrow are composed of myeloid cells which resemble plasma cells On rare occasion the myeloma may be solitary and amenable to surgical extirpation as illustrated by a case previously reported by the writer The patient, a white male fifty eight years of age, was found to have at operation a solitary myeloma of a rib It was excised successfully Three years later the patient died of coronary thrombosis without clinical evidence of recurrence of the disease I have since encountered a similar instance (Figures 16 A and B) Galagno believes that, so called, 'solitary myeloma' if followed long enough, will eventually become multiple As illustrated in Figure 16, when a myeloma involves the thoracic cage, the growth seldom invades the pleura or lung but simply displaces the latter Much more often there is diffuse myelomatosis of bone marrow In addition to skeletal involvement, which often results in pathologic fractures, the diagnosis rests on the finding of Bence-Jones proteinuria, anemia, nephritis and azotemia, in one combination or another

Of particular interest, from the viewpoint of the present discussion, is the frequency of pneu-



Figure 15 Chronic myelogenous leukemia with intrathoracic lesions A (*Left*) Minute infiltrations scattered throughout right lung especially upper lobe infiltrations and linear striations in left lower lobe, enlarged hilar lymph nodes B (*Right*) Lung detail (Patient died Histologic examination of lung tissue revealed immature myeloid cells and polymorphonuclear cells in perivascular and peribronchial tissues thickened interlobular septa permeated with similar cells myeloid cells in capillaries and in walls of bronchi hilar and tracheobronchial lymph nodes enlarged and invaded by many myeloid cells)



Figure 16 Myeloma with intrathoracic lesions A (*Left*) Well demarcated density in right upper lobe at level of third rib anteriorly circumscribed rounded density in right paravertebral gutter at level of T3 and 4 fractures of right and left lower ribs localized bulging of diaphragm B (*Right*) Oblique view showing position of the two masses (At operation well circumscribed soft hemorrhagic fleshy tumors were found situated peripherally at the sites indicated related to rib structures The chest wall lesion was internal to ribs and external to pleura and lung The lesion in the paravertebral gutter was also external to lung and pleura Contiguous ribs were eroded and showed pathological fractures. Both tumor masses were excised The histologic picture was in keeping with a plasma cell myeloma)

monia in patients with multiple myeloma Zinneman and Hall reviewed the clinical records of sixty four patients with multiple myeloma Thirteen had bouts of bacterial pneumonia and in ten of these it was recurrent A man of sixty three was recently admitted to the Montefiore Hospital with complaints of cough, fever and chest pain During a period of four years this patient had been treated for multiple myeloma and on six occasions had been hospitalized with clinical and chest x ray findings in keeping with transient episodes of pneumonia Pneumonia and bronchiectasis are also a feature of agammaglobulinemia because of poor antibody response to infection

Infectious Mononucleosis

Glandular fever or infectious mononucleosis is, in the vast majority of cases, a self limited disease occurring sporadically or in small epidemics The intensity of the seizure varies considerably in different individuals and is apt to be more acute during epidemics The disease is most likely caused by a virus although a specific agent has not been isolated Infectious mononucleosis affects mainly young people, in fact, the most detailed studies of the disease have been made in Army station and Veteran Administration Hospitals To explain the unusual age incidence, the increased seasonal incidence the fruitless results of attempts at experimental transmission and the absence of transmission to room-and ward mates Hoagland postulates that the disease is transmitted chiefly by oral contact which allows for salivary exchange and that the incubation period of the disease is about thirty three to forty nine days

Infectious mononucleosis, in its classical form, is characterized by fever, malaise, sore throat, enlargement of lymph nodes, splenomegaly, skin eruptions and abdominal complaints. The disease is protean in its manifestations and may involve diverse organs, including the central nervous, cardiovascular, digestive and respiratory systems as well as hematopoietic organs.

As the name implies, infectious mononucleosis is featured by hematologic findings. The characteristic cell of infectious mononucleosis is an immature, "leukocytoid" lymphocyte which is present in lymph nodes, tissues, bone marrow and blood. The lymphocytes vary in size, in the appearance of the cytoplasm, in the size and shape of the nuclei and in their ability to take up stain. The mononuclear count is usually much higher in sporadic cases than during epidemics. In a study of 556 cases observed in a military hospital, Wechsler and co-workers found an initial, transient leukocytosis, varying between 10,000 to 20,000 cells, or a normal count, followed by a drop to either normal or leukopenic values. An increase in mononuclear cells was usually evident after the third day of the disease, the percentage ranging in most instances between forty and fifty. Schultz and Hall, in a study of 100 cases, found that during convalescence there is occasionally an eosinophilia.

In addition to the physical and hematological findings, the heterophile antibody agglutination test of Paul-Bunnell, using sheep cells, is a valuable diagnostic aid. It should be noted that the test has been found positive in high titre in a considerable number of other diseases. The Davidsohn absorption tests, using guinea pig kidney and boiled beef erythrocytes, is of additional value. A frequent observation is an abnormally high incidence of disturbed liver function found in as high as 90 per cent of the cases. Sera of patients with infectious mononucleosis may give false positive reactions for syphilis, typhoid and undulent fever. As might be expected, the differential diagnosis often includes enteric diseases as well as acute leukemia, poliomyelitis and infectious hepatitis.

Respiratory tract involvement, although seldom striking, occurs quite often. The most frequent symptoms, aside from those referable to the throat and upper air passages, are croupy cough, wheezing respiration and substernal discomfort. These are often related to enlarged hilar lymph nodes. In addition, there are symptoms indicative of tracheitis and bronchitis. In a few, signs of pneumonia may be present with high fever, chill and evidence of pulmonary consolidation. As a rule, the physical findings of pulmonary involvement are minimal and do not parallel the extent of the roentgen changes. In fact, the chest x-ray may reveal abnormal findings in the absence of clinical signs.

The chest x-rays may reveal enlarged hilar lymph nodes, often in association with perivascular patchy infiltrations in both lungs. Occasionally, there may be massive densities. McCort studied the chest x-ray findings of forty-three patients with infectious mononucleosis. In six patients there were changes which could be attributed to the disease. An additional case studied on another occasion was included in the group. Enlargement of the mediastinal lymph nodes were noted in two cases. Both enlargement of the mediastinal lymph nodes and pulmonary parenchymal changes were noted in three cases. Parenchymal changes only were noted in two cases. Wechsler and co-workers found, in fourteen of 556 cases of infectious mononucleosis, roentgen changes in the lungs similar to those encountered in primary atypical pneumonia.

The exact nature of the pneumonia occurring in the course of infectious mononucleosis is not always ascertainable since individuals rarely die of uncomplicated disease. In some, the disease represents a secondary infection, in others, the two conditions occur simultaneously, apparently caused by the same agent. Allen and Kellner had a unique opportunity of being able to examine the organs of a pilot who had had a recent seizure of infectious mononucleosis and who died immediately after an aviation accident. A chest x-ray taken at the time of the initial hospitalization revealed a definite increase in the vascular and peribronchial markings of the right lung. The hilar markings were also prominent. The tentative diagnosis was primary atypical pneumonia, etiology unknown. A blood count of 11,450

white cells with 14 per cent neutrophils, 77 per cent lymphocytes and 9 per cent monocytes, as well as the obtainment of the heterophil antibody titer of 1 896, made it evident at the time of hospitalization that one was also dealing with infectious mononucleosis Examination of the lungs after death revealed many nodular collections of mononuclear cells and lymphocytes in relation to bronchi and blood vessels but often within the interstitial tissues In the light of these findings, the authors considered it most likely that the roentgen appearances, ascribed initially to a primary atypical pneumonia, represented mononucleosis infiltrations of the lungs

A detailed review of the pathology of infectious mononucleosis was published by Curtis and Smith The study was based on nine autopsies, including the one of Allen and Kellner cited above, also the examination of more than 100 lymph node biopsies and additional material obtained from the files of the Army Institute of Pathology *With respect to the respiratory tract* it was noted that in two cases there was frank pneumonic consolidation, the cellular exudate in one being of the polymorphonuclear neutrophil type and in the other of the large lymphoid type Most cases showed exaggeration of the peribronchial and bronchial tissues and, in some, the round cell reaction extended along the intra alveolar septa to simulate interstitial pneumonitis The *actual involvement of lung tissue was slight in five, prominent in three and absent in one These authors also draw attention to the frequency of* symptoms and signs of atypical pneumonia in patients with infectious mononucleosis, especially at the onset of the disease

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Allergic Diseases

Introduction

THE NUMBER of diseases ascribable wholly or in part to allergic causes is considerable and the list is growing. It has been estimated that approximately 10 per cent of the population suffers from some form of hypersensitivity, chiefly bronchial asthma and hay fever. Of those normally non-allergic many become sensitized after injections of antitoxin or serum or after medication with various drugs. Since the introduction of sulfonamides, penicillin, streptomycin and other antibiotics, increasing numbers are also developing sensitivity to these agents. Brown published an *abbreviated* list of 217 drugs and antibiotics which have been found to be associated with allergic reactions. This investigator believes that approximately 500 different drugs can be proved to be sensitizing substances. Even the use of ACTH and cortisone to combat hyperergic states may in turn cause allergic reactions. It is obvious, therefore, that allergic diseases constitute a sizable segment of human illness.

Tissue Changes in Allergy

Allergy is not simply an expression of the union of allergin and reagin but, as Selye and others have pointed out, a complex biochemical phenomenon triggered by a host of stimuli which call forth a pituitary adrenal reaction in response to stress. The characteristic allergic reaction is featured by a sudden, often explosive onset, rapidly reaching a climax and a slow resolution. Although as a rule the tissue changes parallel the intensity of the reaction, there may be considerable variation. At one extreme one meets with violent functional derangements, even sudden death, without demonstrable changes in the tissues, as may occur in anaphylactic shock; at the other, with acute reversible inflammatory changes which the individual is able to weather and is left none the worse as a result. Between these two extremes one encounters various degrees of hypersensitivity reactions. It is often difficult to correlate the tissue changes with an allergic cause and this becomes increasingly so with the passage of time. In the scale of allergic reactions there may be degenerative, necrotizing, proliferative and granulomatous changes or a combination of these.

As the various elements entering into the allergic reaction become more complex, especially if the irritation is chronic or of low intensity, and depending on the nature of the shock organs, the tissue changes are apt to lose any distinguishing features. A stage is eventually reached where it becomes impossible to correlate the nature of the tissue changes with hypersensitivity except for indirect evidence in the way of an allergic family or personal history, possibly significant hematologic findings, the response to antiallergic treatment and similar suggestive but inconclusive indices. Finally, one meets with a number of diseases the allergic nature of which is highly speculative. Several of the so-called collagen or hyalinoid diseases to be described later fall in this ill-defined group. There is increasing evidence that hypersensitivity probably underlies the majority of these conditions.

Hypersensitive lungs, like other organs, may react to an excitant with varying degrees of in-

tensity, ranging from an evanescent seizure of bronchospasm to chronic bronchiolar obstruction, transitory or protracted eosinophilic infiltrations often associated with polyserositis and eosinophilia, pneumonia, diffuse vasculitis, interstitial fibrosis or a combination of these and other "morphological equivalents." Sooner or later secondary infection of the lung supervenes and obscures the basic pathological changes. Analogous tissue reactions may take place in other parts of the body concurrently or consecutively which may or may not be clinically apparent. At times, the symptom complexes express themselves in bizarre syndromes. In adulthood the respiratory tract is particularly vulnerable to allergic irritation as exemplified in bronchial asthma and hay fever. With advancing years, the heart and kidneys bear the brunt. The reticuloendothelial system, composed of a reactive group of cells found chiefly in the lymph nodes, spleen, liver, bone marrow and loose connective tissue take an active part.

Bronchial Asthma

Bronchial asthma represents a state of hypersensitivity of the respiratory tract to air borne or blood borne excitants. The disease is brought about by various factors: extrinsic, intrinsic or a combination of both. Studies of the incidence of the various allergies including bronchial asthma, reveal a family history in over 50 per cent. The factor of heredity is strikingly shown in studies of large families whose health records can be traced back for several generations. Particularly revealing is the incidence and types of allergies occurring in single ovum twins. In these, the age of onset of the disease, its severity and the nature of the offending allergens show remarkable parallelisms: the stronger the family taint, the more sensitive the individual to all manner of excitants.

As typified in the allergic skin reaction, the features of which have been studied intensively by Kline, hypersensitivity of lung tissue to an irritant is also characterized by an outpouring of edema fluid. In the bronchi the exudate soon becomes viscid due admixture of mucus from secreting glands. An acute, nonbacterial inflammatory reaction is established around blood vessels. In uncomplicated asthma the vascular response is relatively mild, of limited extent and reversible. In protracted asthma, the vascular response is more profound with eventual desquamation of epithelium, distention of mucous glands, hypertrophy of the elastic fibers and of the circular muscles of the bronchi and dilatation of the bronchioles and alveoli. Secondary infection soon complicates the process. In hyperergic states the perivascular and vascular reactions are intense and are apt to be followed by permanent tissue damage.

It may be mentioned at this point that although an excess of eosinophils in the blood (more than 300 per cu. mm.) as well as in the tissues, sputum, serous effusions and other excreta characterizes the allergic reaction, the absence of eosinophilia does not rule out allergy. In fact, profound hypersensitivity states associated with marked depression of the adrenal cortex may be accompanied by temporary suppression of the eosinophil response. On the other hand, various parasitic infestations, infections, diseases of the hematopoietic organs and even, on rare occasion, malignant neoplasms may be associated with eosinophilia (*see* Table 9).

Clinical Features

The symptomatology of bronchial asthma ranges the gamut of transitory seizures of wheezing to a status asthmaticus. The pulmonary manifestations are related chiefly to bronchial obstructive phenomena caused by sputum retention. The secondary infection of the distal portions of the lung soon gives rise to a symptomatology of its own. The type of asthma, whether it be of the, so called, extrinsic or intrinsic variety, has an important bearing on the course of the disease. Extrinsic asthma is caused by inhalation of pollens of weeds, grasses and trees, dusts, animal emanations and molds. The disease appears at a relatively early age in persons with decided allergic family histories. Additional signs of hypersensitivity are often present in the form of atopic

dermatitis allergic rhinitis drug and food idiosyncrasies Other significant features include the obtainment of positive skin reactions to offending allergens minimal evidence of bronchopulmonary infection and usually a satisfactory response to antiasthmatic medication The prognosis is relatively good

Intrinsic or bacterial asthma is characterized by its appearance later in life in individuals without an allergic background A nondescript respiratory infection often antedates the onset of symptoms After the establishment of the pulmonary infection the individual becomes susceptible to recurring cough expectoration wheezing and increasing dyspnea. The symptoms may be temporarily improved by expectorants and antibacterial treatment seldom by antiallergic drugs Intrinsic asthma carries with it a decidedly worse prognosis than the extrinsic variety because of the repeated damage sustained by the lungs as a result of recurrent infections and the fact that the accompanying fibrosis and emphysema may lead in time to chronic cor pulmonale

ROENTGENOLOGY

The roentgen findings of bronchial asthma the subject in which we are particularly interested at the moment reflect the sequelae of bronchial obstruction and infection also the intensity and duration of these factors The damage sustained by the pulmonary blood vessels is usually minimal and is seldom evidenced roentgenologically However in certain hyperergic states to be discussed later the vascular component may be reflected in certain roentgen changes Chronic bronchial asthma is associated with recurring bronchospasm causing an accumulation of thick tenacious secretion in the air passages The resulting trapping of air in the bronchioles and alveoli beyond the point of obstruction abetted by the reflex narrowing of the air passages during the expiratory phase of respiration lead to a gradual accumulation of air in the alveoli This results in obstructive or so called hypertrophic emphysema the most frequent by product of chronic bronchial asthma

During an acute asthmatic seizure the chest x ray may reveal evidence of acute overdistention of the lungs as seen in the hyperillumination of the lung fields the enlargement of the thoracic cage and depression of the diaphragm the excursion of which is diminished After the subsidence of the initial acute seizures the roentgen markings resume their previous normal state With recurring episodes the hyperillumination of the lungs becomes permanent the ribs occupying a more-or less fixed horizontal position the intercostal spaces becoming wider The vascular and hilar markings become more prominent and there is increasing kyphosis of the chest In the lateral projection the width of the retrosternal space is increased and also shows hyperillumination At this stage one may also discern bullous formations within the lungs and blebs at the periphery In addition to the generalized overdistention of the lung resulting from diffuse obstruction of small bronchi plugs of sputum obstructing bronchi may cause transitory segmental atelectasis (Figure 17) If a large bronchus is involved lobar or massive atelectasis of an entire lung may result

Increasing alveolar distention and disruption may produce large air pockets within the lungs (bullous emphysema) and blebs in the pleura both of which may give rise to complications Advanced degrees of bullous emphysema may give a picture of a vanishing lung Air escaping from ruptured inelastic alveoli may pass along blood vessels and bronchi to the mediastinum causing pneumomediastinum Ruptured blebs on the pleural surface may give rise to pneumothorax on one or repeated occasions Once interstitial emphysema is established air may escape along fascial planes to the neck chest and abdomen giving rise to variable degrees of subcutaneous emphysema In one instance which I had occasion to treat the escaped air could be traced along muscle planes as far down as the lower extremities If the pressure is sufficiently high air may escape into the abdomen and give rise to retropneumoperitoneum A detailed discussion of these and other complications of bronchial asthma including the effects of physiological alterations within the thoracic cage as a result of the emphysematous state is beyond the scope of these pages To illustrate the sequence of



Figure 18 *Case 10* Tension pneumothorax in an asthmatic after an injection of histamine A (*Left*) Pneumothorax collapsing the right lung an air filled bleb is faintly seen at the upper pole of collapsed lung right leaf of diaphragm depressed flattened and showing costal digitations B (*Right*) Five weeks later lung has re expanded

sideration are characterized histologically by an interstitial nonbacterial mononuclear inflammation the latter consisting chiefly of eosinophilic leukocytes serous membrane exudation and variable degrees of necrotizing vasculitis especially of the small arteries The involvement of the latter determines the intensity and permanence of the tissue damage Roentgenologically these conditions are featured by diffuse infiltrations of patchy or massive proportions and transient pleural effusions A characteristic feature is the presence of eosinophilia also a high eosinophil content of the serous effusions sputum nasal discharges and other body fluids

Transitory Pulmonary Infiltrations and Eosinophilia (*Loeffler s Syndrome*)

The association of fleeting infiltrations in the lungs and eosinophilia was brought to general medical attention by Loeffler in 1932 The condition has since been referred to as Loeffler s syndrome although there are now a number of variants of the original description Under an all inclusive title infiltrative eosinophilia Dias Rivera and co workers list no less than eighteen eponyms for the condition The authors include in this group various parasitic infestations as well as diseases without any recognizable cause For the present we are concerned with such forms of the disease which may be ascribed to constitutional hypersensitivity although a clear cut distinction between the several conditions which may give rise to the disease is not possible on the basis of hypersensitivity alone

The nature of the pulmonary infiltrations in Loeffler s syndrome are detected only in chest x rays often accidentally The infiltrations remain in the lungs for a few weeks and disappear without leaving any trace At times the pulmonary involvement is widespread In the vast majority the infiltrations represent patches of eosinophilic pneumonia in allergic individuals a history of bronchial asthma being often obtained As mentioned an excess of circulating mature eosinophils in the blood is a feature of the disease The blood eosinophilia may reach as high as 70 per cent of the total leukocyte count more often the eosinophil percentage is in the neighborhood of twenty The leukocyte count is

moderately increased The following case is a typical example

Case 11 Male—Age 7 years

A Negro boy with a history of repeated seizures of bronchial asthma was admitted to Seton Hospital for treatment of suspected pulmonary tuberculosis In the three months previously the patient had been treated in another institution for a respiratory infection characterized by shortness of breath wheezing fever and nonproductive cough The chest x ray findings were interpreted as representing patches of bronchopneumonia involving especially the right midlung For a time the chest x rays showed clearing but the infiltrations soon recurred

The day after admission to Seton Hospital the boy became acutely ill with a typical asthmatic seizure associated with wheezing and fever The symptoms responded to antiasthmatic treatment over a period of two weeks Of particular interest were the chest x ray and laboratory findings Prior to the seizure the chest x ray showed increased hilar markings in both midlung regions and hyperillumination of the lower lung fields Nine days later at the height of the asthmatic seizure an irregular circumscribed density was seen in the right hilar region extending into the midlung Eleven days later the density had almost completely absorbed leaving increased bronchovascular markings (Figure 19)

The following laboratory studies were most instructive A bronchoscopy was negative Mantoux tests in strengths from 1 10 000 to 1 100 tuberculin were negative Gastric cultures were negative for acid fast organisms There were no parasites ova or occult blood in the stools The blood count revealed a leukocytosis ranging from 11 000 to 20,000 with an eosinophilia ranging from 13 to 70 per cent The total eosinophil counts ranged from 154 000 to 160 000 cells per cu mm The nasal discharges revealed 8 per cent eosinophils The patient remained at Seton Hospital for two months and was discharged with a diagnosis of Loeffler s syndrome

The syndrome associated with Loeffler s name has been found in a number of diseases including infestations with various parasites fungi and higher bacteria the inhalation of plant pollen and other agents commonly found in an analogous condition so called Tropical Pulmonary Eosinophilia Some authorities are of the opinion that even in the presence of specific agents such as those mentioned the mechanism is essen

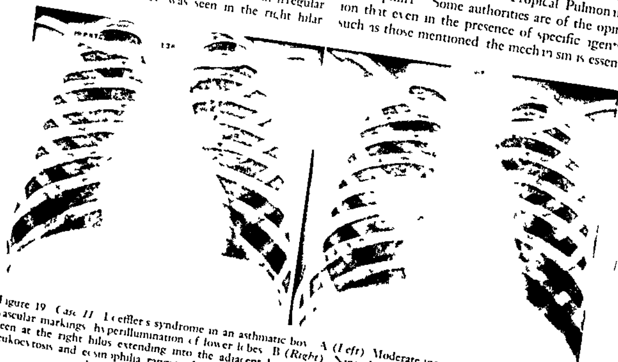


Figure 19 Case 11 Loeffler s syndrome in an asthmatic boy A (*Left*) Moderate increase in hilar and bronchovascular markings hyperillumination of lower lobes B (*Right*) Nine days later an irregular density is now seen at the right hilus extending into the adjacent lung field (At the height of the seizure there was moderate leukocytosis and eosinophilia ranging from 13 to 70 per cent Eleven days after B the density had almost completely disappeared leaving exaggerated hilar and bronchovascular markings)

tially allergic in nature since transient pulmonary infiltrations have been produced experimentally by parenteral injection of extracts of these agents in sensitized animals Furthermore, these pulmonary infiltrations have been found to disappear temporarily after injection of epinephrin

Loeffler's syndrome may be encountered in children as well as in adults Schechter and Graub reported the condition in twins two years of age Instances of Loeffler's syndrome have been described in association with various visceral involvements including that of the liver, stomach and other organs

Zuelzer and Apt draw attention to the fact that, in contrast to the picture of Loeffler's syndrome in adults in which there is eosinophilia and leucocytosis of usually moderate degree and with predominantly pulmonary localization, in young children, the process is likely to affect the liver and is apt to be associated with a greater disturbance in the blood picture Engfeldt and Zetterstrom also consider disseminated visceral lesions, associated with extreme eosinophilia, another facet of polyarteritis nodosa, featured by allergic granulomatoses and necrotizing lesions They call the syndrome, 'Disseminated Eosinophilic Collagen Disease' (*see* Chapter 6)

In the differential diagnosis of Loeffler's syndrome, it should be mentioned that many individuals are currently being treated with sulfonamides, penicillin, streptomycin, liver injections and other drugs which are allergizing agents and often associated with eosinophilia An intercurrent atypical pneumonia, during treatment of a patient receiving such medication, may be mistaken for Loeffler's syndrome I have been puzzled by several such experiences

That the pulmonary infiltrations in Loeffler's syndrome represent, in most cases, areas of eosinophilic pneumonia is substantiated by a number of reports describing the disease in patients who died accidentally In four cases Meyenburg found the lungs to contain eosinophilic leucocytes and giant cell infiltration, marked interstitial proliferation and serous exudation This investigator also noted minute granulomata and vascular alterations, the significance of which will become apparent later in discussions of rheumatic pneumonia and polyarteritis nodosa It should be noted, however, that Viswanathan suspects that the cases reported by Meyenburg may have been instances of tropical pulmonary eosinophilia

A case, with autopsy findings reported by Bayley and co workers revealed lesions consisting of pneumonic exudate containing large numbers of eosinophils These investigators were impressed with the advanced stage of organization of the exudate, the presence of small granulomatous lesions and the occurrences of necrotizing arteritis and phlebitis Fibrinoid swelling and necrosis of collagen were very prominent features and suggested an allergic basis One gathers from these observations as well as those of Harkavy, Bergstrand and others, that even in presumably benign forms of Loeffler's syndrome the tissues may sustain vascular damage

As a rule, eosinophilic pulmonary infiltrations of the type described cause minor complaints consisting of cough, headache, low grade fever and other catarrhal symptoms Often there are no complaints at other times, as in the case previously cited, the symptoms are hyperacute and in a few, the course is protracted The physical signs in the chest, if present, are minimal and non informative of the true nature of the disease The appearance of the chest x ray, especially serial x rays, and the finding of eosinophils in the blood, are decisive in diagnosis The lungs reveal irregular densities of a soft appearance either

may take a week or several weeks, usually less than a month A pleural effusion may be present In some cases the chest x-rays show massive involvement Upper lobe infiltrations, persisting for several weeks or months, may simulate tuberculosis In fact, Loeffler in his original description of the condition, considered tuberculosis in the differential diagnosis Lower lobe infiltrations simulate atypical or viral pneumonia In a case reported by Elkeles and Butler, a transient apical cavity was found in a young soldier The presence of eosinophilia, the absence of acid fast organisms in the sputum and the later appearance of fleeting pulmonary infiltrations led the au-

thors to conclude that the cavity was probably an area of resolution in an eosinophilic lung.

A most instructive case was reported by Buckles and Lawless. A man of fifty nine was found to have a density in the right upper lobe suggestive of a carcinoma. The sputum and bronchoscopic aspirations revealed monilia albicans on culture; also eosinophilia. Cells were found which were very suggestive of cancer cells. The blood count revealed 12,100 leukocytes with 43 per cent eosinophils. Because of the persistence of the mass and the finding of cells suspicious of carcinoma, a pneumonectomy was done. The examinations of the specimen revealed tissue changes compatible with Loeffler's syndrome. The microscopic features were fibrosis with massive infiltrations by eosinophils; also polyarteritis with eosinophils, granulomatous areas, endothelial cell proliferation with giant cells and mononuclear cells. Later studies showed a gradual reduction in the leukocyte and eosinophil counts with a return to normal figures within three months of the operation.

The allergic nature of Loeffler's syndrome finds additional support in the response of the disease to hormonal treatment. The administration of ACTH or cortisone causes a rapid fall in circulating eosinophils and radiographic clearing of the pulmonary infiltrations. Harkavy reported four cases of hyperergic vascular disease characterized by extensive purpura, pulmonary infiltrations with eosinophilic myocarditis, hepatosplenomegaly and renal involvement. Treatment with cortisone and ACTH was effective in controlling the reversible phases of the disease such as eosinophilic pulmonary infiltrations, purpura, joint pains and fever. It failed to halt the irreversible lesions in the heart and kidneys. Similar experiences of the striking beneficial effects of cortisone and ACTH in the treatment of Loeffler's syndrome have been reported by others.

Severe Forms of Pulmonary Infiltrations and Eosinophilia

The patients in this group are more acutely ill and for longer periods. They usually have more extensive pulmonary involvement often complicated by pleural and pericardial effusions. The patients are more apt to show hyperergic manifestations in other organs and evidence of polyarteritis on histological examination of tissues. The accompanying eosinophilia is usually more pronounced, although in some the hematological findings are remarkably inconspicuous. The acute symptoms as well as the reversible elements of the pathological process are often controlled by ACTH or cortisone treatment.

Harkavy has stressed the importance of vascular allergy in the pathogenesis of bronchial asthma associated with recurrent pulmonary infiltrations and eosinophilic polyserositis. Since 1941 his thesis has been that not only the bronchi and other parts of the lungs may be involved in vascular reactions but also the myocardium, serous membranes, joints, skin, nervous and hemopoietic systems. These syndromes are determined by the number, character and variations in the combinations of the shock tissues affected. Thus there may be a pulmonary, myocardial, a pleuropulmonary, myocardial or a pleuropulmonary myopericardial response, the latter resulting in some cases in a picture of constrictive pericarditis. With the extension of the process to all the serous membranes the characteristic symptoms of polyserositis appear. In the presence of these fundamentally allergic responses, disturbances in the dynamic aspects of the circulation are inevitable. Although these symptom complexes are often described as clinical entities, Harkavy emphasizes that they are not of independent origin but are merely varying expressions of a state of hypersensitiveness.

The more severe forms of hyperergic diseases which fall into Harkavy's group of patients have been documented under various titles such as "Loeffler's Syndrome with Associated Eosinophilic Pleuritis," "Eosinophilic Pleural Effusion and Pericarditis with Effusion in an Allergic Subject," and "Transient Periods of Cardiac Enlargement Associated with Hypersensitivity to Different Etiologic Agents." In addition to reports such as those mentioned, it is noteworthy that in a number of cases of so-called acute primary or idiopathic pericarditis the authors draw attention to the frequent coexistence and

occasionally recurrence of pulmonary and pleural lesions At times one even obtains an allergic history and an excess of eosinophils in the blood It is suspected that in some instances idiopathic pericarditis is a manifestation of allergy representing a hypersensitive response of the pericardium to an upper respiratory tract infection Idiopathic pericarditis is a benign often recurrent disease frequently associated with effusions in other serous membranes Moehlig and Steinbach stress the possible role of the adrenal cortex in causing peritoneal pleural and pericardial effusions by interfering with water and electrolyte metabolism

The course of the disease in the following patient illustrates graphically the thesis under discussion In slightly over a year a man of thirty seven developed five seizures of pulmonary infiltrations pleuritis and/or pericarditis The pleural fluid as well as the peripheral blood showed a preponderance of eosinophilic leukocytes The acute febrile seizures were accompanied by chest pain a pericardial friction rub and electrocardiographic evidence of pericarditis Improvement followed ACTH and cortisone treatment

Case 12 Male—Age 37

A dejected alcoholic stutterer had been afflicted since childhood with petit mal sinus trouble dizziness tinnitus and abdominal pain In June 1950 he was admitted to a hospital with cough expectoration chills fever and left sided chest pain A chest x ray revealed cardiac enlargement and infiltrations in both lower lung fields There were healed fractures of a number of ribs The patient improved and was discharged with a diagnosis of left lower lobe pneumonia pleurisy and an enlarged heart In August 1950 the patient had a recurrence of chest pain cough and fever He was rehospitalized and again there were found cardiac enlargement and densities in both lower lung fields A chest x ray taken three weeks later showed a decrease in the size of the heart and practically clear lung fields

In September 1950 November 1950 and February 1951 the patient was treated for chest pain fever and dyspnea On each occasion the heart was found enlarged and infiltrations were present in both lower lobes regressing in about three weeks On May 16 1951 the patient consulted me for a recurrence of the seizure The heart was enlarged sounds distant no murmurs there was a diastolic gallop and a distinct pericardial friction rub heard Blood pressure was 100/60 The chest x ray showed cardiac enlargement The patient was referred to the Montefiore Hospital for further study A chest x ray taken shortly after admission revealed irregular soft infiltrations in the left lower lobe and fluid at both bases The heart appeared slightly smaller than in the film taken five days previously In a short time the chest x ray findings were within normal limits (Figure 20)

Repeated blood counts chemical and serological tests sputum examinations and blood cultures did not contribute significant information The only positive finding was a rapid blood sedimentation rate A bronchoscopy done on June 1 1951 revealed the right main bronchus and subdivisions normal the left lower bronchus appeared inflamed and narrowed The patient ran a low grade fever and continued to complain of chest pain He improved under crystacillin and sedation But soon the symptoms recurred and again the chest x ray showed cardiac enlargement and linear infiltrations in both lower lung fields also fluid at both bases A right thoracentesis yielded 20 cc of thick brown fluid containing 10 per cent eosinophils and large mononuclear cells The fluid was sterile on culture Blood examination revealed the hemoglobin 11 gm red blood cells 3 900 000 white blood cells 9 000 with 62 per cent neutrophils 19 per cent lymphocytes 7 per cent monocytes and 12 per cent eosinophils The sedimentation rate continued rapid Examination of nasal secretion and sputum showed no eosinophils The bone marrow showed a mild increase in eosinophils Total eosinophil counts of the peripheral blood revealed a variation ranging from 737 to 987 cells per cu mm There were no parasites in the stool A tuberculin test was strongly positive in 1 1 000 dilution OT histoplasmin skin test negative trichinella skin test transiently positive trichinella precipitin test negative A muscle biopsy showed normal muscle

Because of the persistent fever moderately high eosinophil count and continued symptoms ACTH was started in doses of 15 mgm every six hours and continued for seven days There was rapid improvement The heart and lungs returned to a normal state the eosinophil count fell to 44 cells per cu mm the sedimentation rate returned to normal very slowly and the electrocardiogram which had previ

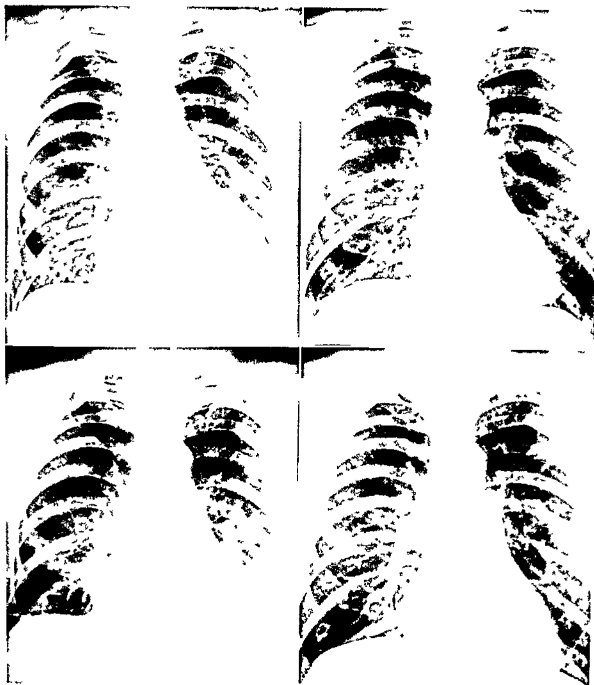


Figure 20 *Case 12* Recurring pulmonary infiltrations, pleuritis and pericarditis with eosinophilia A (*Upper left*) Circumscribed ovoid density in right lower lobe, irregular infiltrations and pleural reaction left lower lobe, heart enlarged, evidence of healed rib fractures on left B (*Upper right*) Three weeks later regression of pleuropulmonary lesions, decrease in size of heart C (*Lower left*) Three months later reappearance of pleuropulmonary lesions at left base, linear striations at right base, heart again enlarged D (*Lower right*) Two weeks later regression of lesions and size of heart (Over a period of fourteen months, five seizures occurred of the type shown, clinical and electrocardiographic evidence of recurring pericarditis, fluid aspirated from both pleural cavities showed an eosinophile count as high as 12 per cent, increase in eosinophils in bone marrow smear and blood, favorable response to ACTH and cortisone treatment)

ously revealed precordial T wave changes, consistent with the presence of pericarditis, resumed a normal pattern

On July 1, 1951 the patient had a recurrence of chest pain, fever and tachycardia Chest x rays revealed cardiac enlargement and a left sided pleural effusion The sedimentation rate increased and the leukocyte count rose to 15,000 with 1 per cent eosinophils A left thoracentesis revealed 300 cc of yellow fluid which was sterile and contained rare eosinophils Examination of the fluid as well as the peripheral blood for lupus cells was negative By July 16, 1951 the heart resumed its normal configuration and the pleural effusion absorbed The patient had mild chest pain and felt weak He was again treated with ACTH, 15 mgm every six hours and gradually increased to 25 mgm every six hours Following this there was steady improvement and gain in weight The eosinophil count throughout this period ranged between twenty two to sixty six cells per cu mm The patient was then placed on a maintenance dose of cortisone 25 mgms four times a day and the medication gradually curtailed Chest x rays in October and November, 1951 showed no new developments

Tropical Pulmonary Eosinophilia

In 1940, Frimodt Moller and Barton studied 600 cases in a tuberculosis sanatorium in India in whom an eosinophilia of over 20 per cent was present They found 175 who not only had eosinophilia but also unusual chest x ray findings which were not characteristic of tuberculosis They termed the condition "Pseudo tuberculosis of the Lung, with Massive Eosinophilia" Three years later Weingarten encountered a similar condition in Bombay, India He designated the disease "Tropical Eosinophilia" to which Ball later added the descriptive, 'pulmonary," to indicate the major recognizable seat of the disease Tropical pulmonary eosinophilia has been described under several other titles Viswanathan, an early student of the disease reported in 1948 observations on 207 cases the majority were army personnel stationed in Assam and Burma He also summarized the findings of 685 cases recorded in the literature

Tropical pulmonary eosinophilia has been encountered mainly in India and Ceylon but a sizable number have been reported from other tropical parts of the world, including the East Indies, Africa, China, Australia and the South West Pacific Islands Sporadic cases have been studied in various parts of Europe and in the United States usually of Army personnel recently stationed in the aforementioned parts of the world

Tropical pulmonary eosinophilia may pursue an acute or chronic course, in the vast majority, the latter Viswanathan subdivides the acute type of disease into a self-limiting variety, in which the condition clears up quickly without treatment, and a variety which goes on to chronocity if left untreated The acute type is featured by a sudden onset with high fever, cough and signs of an acute bronchitis or pneumonia The chronic type is featured by general malaise, lassitude, low grade fever, later cough and periodic seizures of dyspnea which in some cases simulate asthma like paroxysms The chest x-ray reveals mottled infiltrations chiefly at the lung bases The hilar markings are apt to be prominent The disease may be limited to a lobe or a lung or the distribution may be of a miliary type In the chronic stages of the disease, only prominent bronchovascular markings may be seen As pointed out by Westwood and Levine, almost any pulmonary shadow may be a manifestation of the eosinophilic lung syndrome

Various theories have been suggested to explain the cause of tropical pulmonary eosinophilia The fact that a high percentage of cases have positive serological tests for syphilis is suggestive to some that the disease may be caused by a spirochete The possibility that the disease is caused by a parasite appeals to others because mites have been isolated from the respiratory tract of some patients The mites belong to various genera *Tarsonemus*, *Tyroglyphus*, *Glyciphagus* and *Carpoglyphus* Carter, Wedd and D'Abrera examined the sputa of twenty eight patients suffering from respiratory complaints Various types of mites were demonstrable in the sputa of seventeen of the twenty-eight patients In addition, there was an eosinophilia in the blood ranging from 6 to 66 per cent Soysa and Jayawardena reported thirty instances of transient pulmonary infiltrations in Ceylonese sol-

diers The eosinophils in the blood ranged from 33 to 81 per cent Mites of either *Tyroglyphus* or *Tarsonemus* were recovered from eleven sputum specimens of twenty-one cases examined In a study of eight cases, Van der Sar was able to demonstrate mites in the sputum of each confirming the studies of others that the condition may be a form of pulmonary acariasis Coutinho considers the disease a distinct entity probably caused by an infectious agent

Pulmonary infiltrations associated with eosinophilia have also been encountered in individuals infested with other parasites including *Entamoeba Histolitica*, liver flukes, trichinella and *Strongyloides intestinalis* The condition has been observed in association with brucellosis coccidioidomycosis and filariasis A frequent cause of transient pulmonary infiltrations and eosinophilia, encountered in the southeastern coastal regions of the United States is creeping eruption or cutaneous helminthiasis

Tropical pulmonary eosinophilia is often indistinguishable from Loeffler's syndrome In fact, some writers believe that the two are synonymous Loeffler's original description referred to a type E possessing features resembling those of tropical pulmonary eosinophilia Physicians who believe that Loeffler's syndrome and tropical pulmonary eosinophilia represent different diseases are impressed with the more protracted course of the latter the presence of an enlarged spleen, the high incidence of positive serological tests for syphilis, positive cold agglutinins, the demonstration of parasites in the sputum or stools and the response to treatment with arsenic Tropical pulmonary eosinophilia responds, often dramatically, to organic arsenic given by mouth (Carbarsone) or intravenously (neoarsphenamine) Treatment with corticotropin has been found to exert transitory improvement However Sanjivi and co-workers are sufficiently impressed with the beneficial effects of ACTH and cortisone to conclude that tropical eosinophilia is a collagen disease or a state of allergy

A scarcity of autopsy material has hampered a definitive understanding of the nature of tropical pulmonary eosinophilia An unusual instance of chronic eosinophilia in a two year old Negro boy in whom the disease was associated with reversible necrosis of the liver confirmed by exploratory laparotomy on two occasions, also pulmonary infiltrations, anemia and ascaris infestation, impressed Perlingiero and Gyorgy with the possibility that the pulmonary infiltrations and eosinophilia as well as the liver involvement found in the child, could be explained on the basis of an allergic response to ascaris toxin But, in a careful study of four children with similar hepatic and pulmonary findings, Zuelzer and Apt concluded that the evidence was equally strong that the disease represented an unusual form of Loeffler's syndrome

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Chapter 6

Allergic Diseases (Concluded)

The "Collagen" Diseases

A HETEROGENEOUS group of conditions have been linked together under the term, "collagen" diseases These entities are probably of diverse origin in spite of the fact that they possess common histological features as well as merging clinical patterns Strictly speaking, the collagen diseases include polyarteritis nodosa, acute disseminated lupus erythematosus, scleroderma and dermatomyositis In the course of time, additional entities have been incorporated, including erythema nodosum, rheumatic fever, rheumatoid arthritis, serum sickness, drug sensitization, blood incompatibility in transfusions, acute glomerulonephritis and several others It is well to emphasize, however, that the mere fact that the collagen diseases share certain morphological features does not necessarily imply a common cause, in fact, there are many reasons, clinical as well as experimental, to minimize the significance of this 'catch-all term for maladies with puzzling clinical and anatomical features" (Klemperer) For the sake of convenience only, the collagen diseases which are traditionally associated with skin changes (disseminated lupus erythematosus, scleroderma and dermatomyositis) will be discussed in the section dealing with diseases of the skin

The pathological changes in the collagen diseases involve the connective tissue or the filler between the cellular elements of the body The connective tissue is composed of fibers and interfibrillar substance The substance is derived from mesenchyme, the progenitor of smooth muscle, endothelium and mesothelium Hence the close relationship existing between the several conditions mentioned previously, also the predilection of the collagen diseases for blood vessels and serous membranes Various aspects relating to the pathological changes will be discussed in conjunction with descriptions of individual conditions For the group as a whole, Calkins and Bauer summarize the pathological features of connective tissue diseases as follows

In the initial stages there is an accumulation of a jelly like, stainable matrix consisting of mucopolysaccharides, water and other components The swelling and loosening of the structure of the collagen is associated with the exudative phase of the disease There may or may not be an accompanying fibrinoid reaction in the form of masses of eosinophilic, homogeneous or finely granular material Around the area of the greatest tissue damage, especially around proliferating blood vessels, there is invasion and proliferation of lymphocytes, polymorphonuclear leukocytes, monocytes, eosinophils and plasma cells In time, there is fibroblastic proliferation eventually replaced with scar formation With the exception of fibrinosis and the relatively slow evolution of the process, the pathologic features of connective tissue diseases are similar to those of wound healing

INTERRELATIONSHIP OF THE 'COLLAGEN" DISEASES

As a matter of historical interest, it is noteworthy that for many years pathologists had drawn attention to the presence of arterial lesions suggestive of polyarteritis nodosa in the tissues of patients with rheumatic fever Others had stressed the fact that in a significant number of patients articular and cutaneous lesions are en

countered in polyarteritis nodosa as well as in rheumatic heart disease. Friedberg and Gross described four cases in which the postmortem examination revealed widespread arterial lesions in association with rheumatic fever and rheumatic heart disease, the latter confirmed by the presence of Aschoff bodies in the myocardium. In the early phases of acute disseminated lupus erythematosus and acute dermatomyositis the diagnosis is often acute rheumatic fever or rheumatoid arthritis. Later sections will deal with various problems concerned in differential diagnosis. A striking example of the interrelationship sometimes found between various collagen diseases was recently cited by Garland and Sisson. A patient, male, aged forty, with rheumatoid arthritis died shortly after examination. The autopsy disclosed diffuse collagen disease with (a) polyserositis (peritoneal, pleural and pericardial fluid), (b) rheumatic heart disease (aortic valve stenosis, (c) "wire looping" of renal glomeruli (as in lupus erythematosus), (d) rheumatoid arthritis and (e) polyarteritis nodosa involving the pulmonary, thyroid and testicular arteries.

The close relationship between the aforementioned conditions is supported by the work of Rich and Gregory who showed that the basic pathological features of rheumatic carditis and arteritis can be produced by causing "serum sickness" in rabbits. These investigators also showed that anaphylactic pneumonia, caused by hypersensitivity in man, has the basic characteristics of rheumatic pneumonia. It should be mentioned that some years previously Fried demonstrated "allergic inflammation of the lungs" by means of repeated injections of horse serum into rabbits. The microscopic examination of the pulmonary tissues showed in some instances a preponderance of eosinophilic cells, necrosis of blood vessels resembling "arteritis nodosa" and cellular infiltration producing a condition resembling granuloma.

Polyarteritis Nodosa with Pulmonary Involvement

Pathology

In 1866, Kussmaul and Maier described the gross and microscopic appearances of a disease which they named periarteritis nodosa. With the later recognition that the changes affect all coats of small and medium sized arteries, the more descriptive term polyarteritis nodosa came into general use. In hypersensitivity angiitis, one of the variants of the disease, small blood vessels of any type, including capillaries and venules, may be involved.

The changes in polyarteritis nodosa affect initially the media of the muscular arteries which becomes necrotic and edematous. There is early involvement of the entire vessel wall with infiltration of cellular elements, chiefly eosinophilic leukocytes. As a result of weakening of the vessel wall, small aneurysmal dilatations develop causing nodular changes along blood vessels, hence the original name. The inflammatory process soon extends to the perivascular stroma. Intracanalicular thromboses develop and this is followed by fibrous replacement and occlusion of the lumina of the affected vessels. Recanalization of thrombi often occurs. The weakened wall which has undergone aneurysmal dilatation may rupture and lead to hemorrhage. The occluded arteries cause infarction of the tissues supplied. The perivascular changes, appearing grossly as nodules of varying size along blood vessels, are found chiefly in the kidneys, heart, liver, skeletal muscles and nervous system. Increasing attention is lately being paid to the vascular changes in the lungs.

Pathogenesis

In recent years studies of polyarteritis nodosa have concerned themselves chiefly with the etiology of the disease and the clinical signs which may permit a diagnosis during life. In 1925, Gruber postulated that polyarteritis nodosa is a manifestation of hypersensitivity and that the condition may be caused by a variety of infectious and toxic agents acting on blood vessel walls. This view is supported by the frequency with which bronchial asthma, eosinophilia and other allergic manifestations are found in association with the condition. Additional support is

offered by the studies of Rich and Gregory who noted focal arterial lesions in tissues after experimental induction of "serum sickness" in animals and after sulfonamide hypersensitivity But, inasmuch as polyarteritis nodosa may develop in patients in whom an allergic background is not demonstrable, Zeek and others make a distinction between polyarteritis of the essential or classical type and of, so called, hypersensitivity angiitis Pulmonary vascular lesions are uncommon in polyarteritis nodosa of the essential type but they are frequently encountered in hypersensitivity angiitis Pulmonary lesions are also an integral part of a subtype known as Wegener's granulomatosis (allergic granulomatous angiitis) to which reference will be made later

Blankenhorn and Knowles draw attention to the fact that of late subgroups and bizarre forms of polyarteritis are being reported with increasing frequency since almost any tissue which has blood vessels may be the site of typical vascular lesions The latter may be associated with almost any disease (disseminated lupus, dermatitis herpatiformis, rheumatoid diseases, sarcoidosis, Feltig's, Reiter's, Wegener's and Cogan's syndromes) Furthermore many agents, exclusive of foreign serum and sulfonamides may also give rise to necrotizing angiitides, including mercurial diuretics, penicillin, thiouracil and drugs producing purpura or hemolytic anemia

Clinical Features

As mentioned, for many years polyarteritis nodosa was of pathologic interest only, the disease rarely recognized during life Currently, the disease is being diagnosed with increasing frequency not only when it involves the heart and kidneys, the sites of predilection, but also when it affects the lungs It is beyond the scope of these pages to describe the variegated clinical facets of the disease except to mention that the illness is often acute, occasionally protracted, if the former, it is characterized by fever, chills and prostration Localizing symptoms and signs are related to the nature of the organ or organs predominantly affected by the vascular changes Involvement of the kidneys may present a picture of increasing renal insufficiency leading to failure Myocardial involvement may terminate in cardiac failure Infarction of abdominal vessels and organs may give rise to symptoms and signs of acute mesenteric thrombosis Involvement of the lungs may be reflected in atypical pneumonia Obviously, when there is severe cardiorenal damage, a fatal issue is almost inevitable But there is reason to believe that patients may survive if the disease is localized to organs such as the lungs possessing considerable functional reserve In such, the disease may undergo arrest Klein reported two cases in which apparent recovery took place but in one the disease reappeared after a lapse of twelve years Similar experiences of apparent recovery have been reported by others The following case, under the writer's observation for the past eight years is an example of clinically arrested polyarteritis nodosa but in which the outlook for complete recovery is still in doubt The course of the disease in this patient is in keeping with a hypersensitivity angiitis

Case 13 Male—Age 50

The patient, a tailor, had an allergic family and past personal history On August 12 1946 he consulted his physician because of tingling pain and itching of the hands and a feeling of tightness of the shoulders The face felt flushed and swollen Physical examination revealed congestion and edema of the tufts of the fingers, also redness of the palms of the hands There was definite edema about the eyelids It was suspected that the patient had some form of angioneurotic edema and he was treated with an injection of 0 5 cc epinephrin and capsules of benadryl

The patient returned to his physician six days later stating that he had gone back to work but that the swelling of the finger tips and itching prevented him from holding the sewing needle He had also experienced pain in the joints of the hands elbows shoulders and knees as well as increasing shortness of breath Examination now revealed a dyspneic man, tired looking, with swollen eyelids and swollen, painful joints The temperature was 101 5° On auscultation rales were heard over both lower lobes also altered breath sounds although the patient had no cough or expectoration A chest x-ray taken four days later revealed irregular infiltrations in both lower lobes and a pleural reac-

tion at both bases The cardiac contour suggested poor tone with a possible pericardial effusion (Figure 21A)

The patient was admitted to a hospital and treated for a week with penicillin and sulfadiazine However the fever, pain and finger swelling persisted but the edemea of the face subsided gradually in the course of the following six weeks Soon the swelling and itching of the face and hands recurred and there also appeared swelling of the tongue and marked elevation of temperature The patient was then treated with streptomycin but this had to be discontinued because of hyperpyrexia and severe constitutional reactions

The course of events following this episode was characterized by slight unproductive cough remittent fever swelling and vague pains in the joints and generalized malaise The chest x rays at first were in keeping with a bilateral bronchopneumonia and fluid at the bases Repeated examinations of the sputum for acid fast organisms and fungi were negative Cold agglutinins blood cultures and biopsy of an epitrochlear lymph node were noninformative Agglutination tests for the typhoid group of organisms were also negative Significant findings were the presence of a relatively low leukocyte count ranging around 8 000 cells and containing 4 to 6 per cent eosinophils also a rapid blood sedimentation rate A chest aspiration revealed an exudate with a preponderance of eosinophilic leukocytes

Since January 1947 the patient has been seen by me several times a year The course of events has been characterized by moderate cough dyspnea on exertion weakness of the hands and occasional eczematoid eruption with oozing and itching of the finger tips On auscultation fine rales are always audible over both lower lungs The blood sedimentation rate continues to be elevated Serial chest x rays have shown a decrease in the patchy infiltrations and absorption of the pleural exudate and in their place a diffuse interstitial fibrosis of a reticular character (Figure 21B) A muscle biopsy done in February 1952 failed to reveal vascular lesions A lung biopsy showed the pleura thickened somewhat edematous with increased numbers of capillaries also fibrous thickening of alveolar walls increased vascularity and cellularity of interalveolar septa, also cellular infiltration around bronchi and into alveolar spaces all monocytic also conspicuous thickening of the wall of small arteries

Since vascular damage is the basic feature of the disease which may affect various organs of the body it is understandable why polyarteritis nodosa may assume diverse clinical disguises The evolution of the disease ranges from that of an acutely progressive and fatal illness as exem



Figure 21 *Case 13* in both lower lobes out both lungs, espec rosis and progressive

plified in its 'classical' form, to a relatively indolent and localized granuloma. In a case of necrotizing angiitis reported by Kampmeier and Shapiro, the patient showed over a span of twenty years evidence of dermatomyositis on one occasion, disseminated lupus erythematosus on another and polyarteritis nodosa on still a third. When the patient died the only evidence of the disease, demonstrable at autopsy, was in a section of hemorrhagic rectus abdominis muscle. Thickened small arteries were conspicuous in the heart, gallbladder, intestinal tract and kidneys.

The more important laboratory findings of polyarteritis nodosa include the presence of hypochromic anemia, leukocytosis, eosinophilia in the presence of bronchial asthma, an elevated blood sedimentation rate, occasionally a false positive serology, albuminuria, hematuria and systemic hypertension indicative of renal damage and abnormal electrocardiographic tracings indicative of cardiac involvement. Of the greatest value is biopsy confirmation obtained from specimens of the skin or other tissues but such proof is available in only a small percentage of cases.

Pulmonary Lesions

Polyarteritis nodosa in its classical form does not involve the blood vessels of the lungs as nearly as often as those of the kidneys, heart and other organs. When the lungs are involved, the symptoms are apt to be overshadowed by the more profound disturbances caused by cardiorenal disease. More often symptoms referable to the respiratory tract are caused by congestive heart failure. Harris and co-workers found the lungs involved in 25 per cent of the cases and somewhat higher percentages of pulmonary involvement have been reported by others. Griffith and Vural noted that among seventeen patients with polyarteritis nodosa, in whom the diagnosis was confirmed at autopsy, in eight a clinical diagnosis was made of pneumonia, bronchopneumonia or pulmonary infarction. The majority complained of dyspnea, chest pain and cough. Liban and co-workers reported the case of a nine month old infant with polyarteritis nodosa. The lesions were in the healed or healing stage of the disease and confined predominately to the lungs and heart. These authors state that about 110 cases of the disease have been reported in children under fifteen years of age. Of these, only ten cases have occurred during the first year of life.

The changes in the lungs resulting from polyarteritis nodosa partake much of the features characterizing the disease in other organs. The gross appearance of the organs may be quite deceptive. Only the histologic examination reveals the true nature of the disease. The most frequent findings are whitish nodules along the small arteries, particularly in the hilar region. Ellman and Cudkowicz believe that the vascular occlusive changes are chiefly in the territory of the bronchial arteries and that the lung changes may represent the effects of progressive pulmonary ischemia resulting from the loss of a bronchial arterial blood supply. Braunstein points out that many of the reported cases are based entirely on clinical evidence. This investigator documented six cases of periarteritis nodosa limited to the pulmonary circulation. In each instance there was also pulmonary hypertension, three of these being associated with mitral stenosis, one with congenital absence of the interatrial septum, one with multiple thrombotic occlusions of small pulmonary arteries and in one the pulmonary hypertension was of unknown etiology. In this localized form of arteritis, Braunstein found the pulmonary arteries chiefly affected. The cases reported in the literature of periarteritis nodosa limited to the lungs have also occurred in patients with pulmonary hypertension. Bank studied forty-two cases in which the autopsy diagnosis was periarteritis nodosa. He noted that in patients with malignant hypertension the lungs were rarely involved. On the other hand, in a group with idiopathic periarteritis, the lungs were frequently involved.

Lyall noted that sections of lung may show a normal pulmonary artery lying adjacent to a diseased bronchial artery. Conversely, in rheumatic lungs the necrotizing arteritis, closely resembling polyarteritis nodosa, involves the pulmonary circulation to the exclusion of the systemic one. In the cases described by Banowitch, Polayes and

Charet the pulmonary arteries showed acute inflammatory infarcts extending to the pleural surface. The parenchymal lesions may be acute granulomatous or healed. The granulomatous lesions are characterized by giant cells of the Langhans type, macrophages and eosinophilic leukocytes. The infarcts secondary to arterial lesions may show various stages of healing, large infarcts at times showing central cavitation.

There is a form of vascular disease so called Wegener's granulomatosis which is characterized by necrotizing granulomatous lesions of the upper as well as the lower respiratory tracts, generalized arteritis and focal glomerulitis. The vascular involvement is chiefly of the small vessels, which show acute and healing lesions in all stages. Renal lesions are a regular occurrence. Wegener's syndrome is generally considered a disease of hypersensitivity. In a detailed description of this disease Fahey and co-workers reviewed twenty-two cases reported in the literature, chiefly in journals of pathology, and added seven of their own. Wegener's granulomatosis, although rare, evinces a predilection for the respiratory tract.

I had occasion to follow the course of a Puerto Rican female, age twenty-three, in whom the clinical and autopsy findings were in keeping with Wegener's syndrome. The patient had asthma since childhood. Five weeks prior to admission to Lebanon Hospital on June 22, 1953, she became ill with fever, cough and chest pain, and on one occasion had bloody sputum. The patient was acutely ill, emaciated, very pale and complained of weakness, epigastric pain, pain in the forearms, back and ribs. The physical examination revealed rhonchi and crepitant rales through both lungs, but no distinct evidence of consolidation. The chest x-ray revealed numerous small infiltrations in both lungs, especially the bases. The spleen and liver were palpable. Various laboratory tests were done, including blood cultures, blood chemical analyses and LE tests, but all were noninformative. The blood count revealed severe anemia and leukocytosis with persistent eosinophilia of 18 to 38 per cent. The urine showed 4 plus albumin, red blood cells, white blood cells and casts. A skin biopsy revealed one small unidentifiable granuloma, but the significance of this finding was not fully appreciated until the post mortem examination.

The patient gradually developed increasing azotemia, edema of the face and sacrum. Late in the disease the patient developed pustular lesions around the nose and lips, also ulcerative nodules on the forehead, upper lip, arms, elbows and buttocks. The patient received blood transfusions, penicillin, streptomycin, iodides, ACTH and cortisone, but the course was relentlessly downhill and she expired on the 110th hospital day.

The autopsy performed by Dr. J. C. Ehrlich revealed fresh ulcerations in the mucosa of the larynx, trachea and main bronchi. There were acute and chronic hemorrhages in the lungs. There was edema of the pulmonary septa and Masson bodies were found. In addition there was disseminated necrotizing angiitis with extravascular and necrotizing granulomas, especially on the face, trachea, breasts, small intestine and spleen. There was diffuse glomerular involvement which caused the renal failure and uremia. There were several ulcers in the duodenum due to artery occlusion at the base of each ulcer.

Parkin and co-workers draw attention to the recurrent and severe pulmonary hemorrhages which may occur in the presence of necrotizing pulmonary alveolitis. In seven patients believed to have had hypersensitivity states as evidenced by glomerulonephritis in each instance and polyarteritis nodosa in four, hemoptysis was a prominent clinical feature. Pathologically the pulmonary lesion was characterized by an acute necrotizing alveolitis which bore certain similarities to the pulmonary lesions described in hypersensitive animals and humans. It is noteworthy that the pathologic findings in Wegener's granulomatosis, as detailed by Fahey and co-workers, showed active and healed necrotizing inflammatory lesions of small arteries and veins and their sequelae in the form of infarcts, hemorrhages, thromboses and aneurysms. In fact, in two cases hemoptysis was among the initial complaints. The cases described by Parkin and co-workers resemble closely those reported showing Wegener's syndrome. In fact there is





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Rheumatic Pneumonia

Rheumatic pneumonia is believed to be an expression of hypersensitivity to a hemolytic streptococcal infection. In about 90 per cent of patients with rheumatic fever there is serologic evidence of a preceding infection with this organism, as shown either in an elevation of the antistreptolysin—O titre or other tests for antibodies. Rheumatic pneumonia is not a clear cut pathological entity. By the time the lungs are examined at autopsy the organs are edematous, congested and often the seat of extensive infarction. In fact, some investigators consider rheumatic pneumonia the result of a combination of rheumatism and congestive changes. In any event it is estimated that rheumatic pneumonia occurs in only about 5 per cent of patients with acute rheumatic disease. Rheumatic pneumonia is characterized histologically by thickening of alveolar walls and interstitial tissues, intraluminal exudates, hyaline membrane formation, vascular and perivascular lesions and, on rare occasion, Masson bodies, the counterpart of Aschoff bodies, which are small granulomas in alveolar ducts and alveoli.

The clinical features of rheumatic pneumonia vary widely depending on the nature of the rheumatic manifestations, the competency of the heart and the status of the pulmonary circulation. The pulmonary symptoms run the gamut from a mild respiratory infection with low grade fever, moderate cough and expectoration to a hyperacute disease with high fever, cyanosis, severe dyspnea, evidence of pulmonary edema and heart failure. In some, the occurrence of rheumatic pneumonia hardly causes a demonstrable increase in symptoms. There is seldom a chill or sudden pain in the chest such as herald most bacterial pneumonias. The physical findings are inconstant and noninformative.

The roentgen features of rheumatic pneumonia are not associated with a sufficiently distinctive pattern to enable one to differentiate the condition from pulmonary congestion which usually coexists to some degree. In the absence of gross evidence of congestive heart failure, the appearance of patchy infiltrations in both lungs particularly in the upper and midportions occurring early in the development of the rheumatic state is suggestive of rheumatic pneumonia. The pulmonary infiltrations may assume miliary or nodular configuration. Inasmuch as bacterial pneumonias are seldom encountered in rheumatic fever, roentgen findings such as those mentioned, occurring in patients with active but not decompensated rheumatic heart disease, should make one suspect rheumatic pneumonia. The course of the disease in the following patient, which was featured by a synchronous and progressive involvement of the heart and lungs, also the autopsy findings illustrate the more important features of rheumatic pneumonia.

Case 15. Female—Age 10

The patient was admitted to the Morrisania City Hospital on December 14, 1947 with a history of cough and fever of four days' duration. The girl appeared acutely ill, irritable and had constant cough occasionally productive of bloody sputum. The physical examination disclosed a loud systolic murmur at the apex and rales throughout the right lung. A chest x-ray revealed the heart moderately enlarged with flattening of the left border. There were no significant lesions in the lungs (Figure 24A).

For a time the patient improved but soon an exacerbation occurred; the temperature rose and the patient became increasingly dyspneic, orthopneic and cyanotic. On auscultation one could now elicit a gallop rhythm, frequent extrasystoles and the murmurs were more pronounced. The chest x-rays revealed the heart increased in size in all chambers and the lungs showed massive irregular densities involving chiefly the midthirds of both lungs (Figure 24B). There appeared increasing edema of the ankles and liver enlargement. Blood cultures were negative. On one occasion a non-hemolytic staphylococcus was found. Spinal fluid was negative. Urine showed albumin 4 plus and numerous red blood cells. Other laboratory examinations were noninformative. The girl went rapidly downhill with increasing evidence of heart failure and died July 11, 1948, approximately seven months after the acute onset of the disease.

The autopsy revealed no pleural adhesions. A



Figure 24 *Case 15* Rheumatic pneumonia in a girl A (*Left*) Heart enlarged with flattening of left border lungs clear B (*Right*) Two weeks later fan shaped, fluffy densities radiating into the central zones of both lungs, marked increase in size of heart (Autopsy showed rheumatic endocarditis of mitral and tricuspid valves congestion and edema of lungs with thickening of septa and mononuclear cell permeation rheumatic pneumonia duration of illness seven months)

small amount of clear yellowish tinged fluid was present in each pleural cavity The lungs were firm but crepitant and floated in water They were patchy, dark and light red with grayish mottling and slightly edematous The bronchi and pulmonary vessels were normal The peribronchial nodes were soft and slightly enlarged The heart was markedly hypertrophied and all chambers were dilated The mitral ring was dilated edges of cups were thickened and verrucous at the coaptation of the border Tricuspid was dilated with verrucae at the border The left ventricle measures 15 mm in thickness the right ventricle 9 mm

Microscopic examination revealed in the lungs the septa thickened by edema and numerous red blood cells The alveoli in scattered areas contained many mononuclear cells some of the larger cells containing brown pigment There was marked congestion Within many of the alveoli edema was present The heart revealed scattered areas of fibrinous collagen degeneration in the myocardium in which Aschoff cells mononuclears and some polymorphonuclear cells were found At the coaptation border of the mitral and tricuspid valves hyalinized nodules and verrucae were clearly seen The diagnosis was rheumatic heart disease enlarged heart mitral insufficiency and tricuspid insufficiency endocarditis, cerebral edema ascites hydrothorax chronic passive congestion of liver and lung and rheumatic pneumonia

Pulmonary Lesions in "Rheumatoid Disease"

"Rheumatoid disease,' according to Ellman is a more descriptive term than rheumatoid arthritis because the former expresses a widespread process affecting not only the locomotor but also other parts of the body In 1948 Gruenwald described a case of rheumatoid disease with visceral lesions and commented that this combination had not been reported previously except for passing mention of nodules in subcutaneous tissues skeletal muscles and nerve trunks, also scars of rheumatic heart disease The case cited had granulomatous lesions in the heart, pleura and capsule of the spleen indicating that all serous membranes may be involved

Baggenstoss, Rosenberg and Hench described thirty cases of rheumatoid disease examined at

autopsy A high incidence of cardiac lesions indistinguishable from those of rheumatic fever was found also a relative frequency of microscopic renal lesions Although pneumonia chronic suppuration embolism and massive collapse of the lung were the most common causes of death the authors could find no distinguishing pulmonary lesions which could be correlated with the rheumatoid disease Nor could they find any relationship between the frequent finding of fibrous pleural adhesions which were present in twenty two of the thirty cases

The Tenth Rheumatism Review published in 1953 contains for the first time three references in which are described five cases of rheumatoid disease with pulmonary lesions In 1954 Harris was able to collect references to a total of twenty cases of pulmonary lesions associated with rheumatoid disease and cited a case of his own Five of these cases had been studied at autopsy two by Ellman and Ball and three by Christie Two additional cases are on record of patients examined at autopsy who showed pulmonary lesions one by Bevans and co workers and the other by Katz and Auerbach Within the space of two years I have had occasion to study six patients with acute rheumatoid disease with characteristic articular manifestations in whom the pulmonary lesions were in keeping with a systemic disturbance In three of these it was possible to obtain lung biopsies for histologic study The roentgenological and pathological findings resembled in some respects those seen in rheumatic pneumonia and in several other members of the collagen group of diseases, also in occasional instances of diffuse interstitial fibrosis

The pathology of the pulmonary lesions in rheumatoid disease has been studied intensively by Christie who describes the histological appearances as follows (a) proliferation of mononuclear cells in the alveolar septa with occasional binuclear formation in the early stages (b) sharply localized areas of fibrinous pneumonia constituting a more severe grade of parenchymatous lesions (c) connective tissue buds resembling those described by Masson and by Neuberger and co workers in rheumatic pneumonia are sometimes present These consist of minute nodules of connective tissue lying in the alveolar ducts budding from the wall (d) focal scars of variable density in the pleura alveolar walls bronchi vessels and peribronchial and perivascular connective tissue Much of the fibrosis is nonspecific although such areas usually contain more advanced foci recognizable as rheumatoid nodules (e) focal scarring or diffuse fibrosis in the walls of the small pulmonary vessels and of the bronchial arteries and (f) acute fibrinous pleurisy and chronic pleural scarring independently of or in association with other pulmonary changes

A study of the pulmonary lesions occurring in rheumatoid disease brings out a number of clinical and roentgenological features in addition to the pathological changes described which would indicate that the pulmonary lesions are part of the same disturbance like the joint lesions The histories of five of the six patients personally studied indicated a preexisting hypersensitivity in the form of urticaria of unknown cause or allergic reactions to sulfonamide or penicillin The case reported by Katz and Auerbach showed sensitivity to iodide In the case reported by Bloom and J H Rubin it was suspected that pulmonary and pleural lesions represented an anaphylactic reaction Levy and Swift reported that the factor of heredity and allergy explained the rheumatoid disease in their patient Ellman and Ball claim that the visceral and other lesions of rheumatoid disease may be explained by hypersensitivity manifestations in tissues The factor of hypersensitivity in rheumatoid disease has been discussed fully in a number of publications by Rich and Gregory and need not be reviewed here The significance of the occasional finding of L E cells in patients with rheumatoid arthritis and other features indicating that rheumatoid disease is apparently one facet of a more widespread systemic disturbance are discussed in various sections of this and later sections

Of particular significance is the time relationship between the appearance of symptoms and signs of rheumatoid disease and the pulmonary manifestations In some the latter appear at the time of recrudescence of joint symptoms In others the joint and pulmonary manifestations



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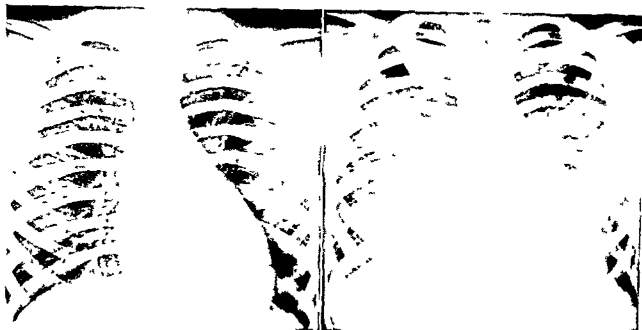


Figure 24 *Case 15* Rh ... border, lungs clear B (*Right*) ... of both lungs, marked increase ... valves congestion and edema of lungs with thickening of septa and mononuclear cell permeation, rheumatic pneumonia, duration of illness seven months)

small amount of clear, yellowish tinged fluid was present in each pleural cavity The lungs were firm but crepitant and floated in water They were patchy, dark and light red with grayish mottling and slightly edematous The bronchi and pulmonary vessels were normal The peribronchial nodes were soft and slightly enlarged The heart was markedly hypertrophied and all chambers were dilated The mitral ring was dilated edges of cups were thickened and verrucous at the coaptation of the border Tricuspid was dilated with verrucae at the border The left ventricle measures 15 mm in thickness, the right ventricle 9 mm

Microscopic examination revealed in the lungs the septa thickened by edema and numerous red blood cells The alveoli in scattered areas contained many mononuclear cells, some of the larger cells containing brown pigment There was marked congestion Within many of the alveoli edema was present The heart revealed scattered areas of fibrinous collagen degeneration in the myocardium in which Aschoff cells, mononuclears and some polymorphonuclear cells were found At the coaptation border of the mitral and tricuspid valves hyalinized nodules and verrucae were clearly seen The diagnosis was rheumatic heart disease, enlarged heart, mitral insufficiency and tricuspid insufficiency, endocarditis, cerebral edema, ascites, hydrothorax, chronic passive congestion of liver and lung and rheumatic pneumonia

Pulmonary Lesions in "Rheumatoid Disease"

"Rheumatoid disease," according to Ellman, is a more descriptive term than rheumatoid arthritis because the former expresses a widespread process affecting not only the locomotor but also other parts of the body In 1948, Gruenwald described a case of rheumatoid disease with visceral lesions and commented that this combination had not been reported previously except for passing mention of nodules in subcutaneous tissues, skeletal muscles and nerve trunks, also scars of rheumatic heart disease The case cited had granulomatous lesions in the heart, pleura and capsule of the spleen indicating that all serous membranes may be involved

Baggenstoss, Rosenberg and Hench described thirty cases of rheumatoid disease examined at

autopsy A high incidence of cardiac lesions, indistinguishable from those of rheumatic fever was found also a relative frequency of microscopic renal lesions Although pneumonia chronic suppuration, embolism and massive collapse of the lung were the most common causes of death the authors could find no distinguishing pulmonary lesions which could be correlated with the rheumatoid disease Nor could they find any relationship between the frequent finding of fibrous pleural adhesions which were present in twenty-two of the thirty cases

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appear at the same time In still others, a non descript "pneumonia" or "pleurisy" precedes for a brief period the joint symptoms and with the appearance of swollen, painful joints, the pulmonary disease appears to become activated The later course of events is characterized by a degree of parallelism in the symptoms referable to both joint and lung lesions

The chest x-ray findings in rheumatoid disease are of major interest since the lung changes portray the dynamic phases in the evolution of the process At times, the pulmonary infiltrations are transitory The most frequent expression of rheumatoid disease in the chest is in a pleurisy, the latter manifesting itself in small serous effusions, large collections of fluid are more apt to be associated with cardiac failure The frequent elicitation of a friction rub on auscultation and the almost inevitable presence of fibrinous or a dense pleural reaction in biopsy or autopsy specimen bears emphasis

The chest x-rays usually show bilateral, more-or-less, symmetrical infiltrations One of the cases described by Christie showed roentgenologically a round, dense shadow 6 cm in diameter in right upper lobe Autopsy revealed it to be a large granuloma with histological features similar to those found in the periarticular nodules of rheumatoid disease The infiltrations may be small and evenly distributed simulating miliary tuberculosis or they may be of a nodular character affecting chiefly the mid and lower lung fields simulating sarcoidosis, inhalational dust diseases or bronchogenic tuberculosis The infiltrations may be irregular and of patchy distribution in keeping with a viral or bacterial bronchopneumonia After the subsidence of the acute stage of the disease, the markings assume a more linear configuration of a delicate or coarse reticular network, such as one sees in lymphangitic carcinomatosis or diffuse interstitial fibrosis of the lungs In long standing disease, secondary bronchopneumonia and suppuration tend to obscure the basic pattern

Caplan described a syndrome in coal workers in which rheumatoid arthritis is associated with nodular fibrosis of the lung roentgenologically similar to, but distinguishable from, the progressive massive fibrosis of coal miner's pneumoconiosis According to Miall, Caplan and co-workers, the pulmonary lesions have no similarity to the interstitial pneumonitis occurring in cases of rheumatoid arthritis, described by Ellman and Ball and referred to previously The 'rheumatoid' lung lesions, described by Caplan, develop fairly rapidly and appear as numerous discrete, rounded opacities scattered diffusely throughout both lung fields The lesions seem to appear in crops, change in size relatively little but may enlarge and undergo cavitation An epidemiological study revealed that whereas rheumatoid arthritis occurs in over 50 per cent of coal-miners with the characteristic lesions, rheumatoid arthritis occurs in only 3 per cent of coal miners with conventional forms of progressive massive fibrosis The exact nature of Caplan's syndrome is still to be determined

There is no characteristic picture typifying the pulmonary lesions in rheumatoid disease But if one views the chest x-ray appearance in the light of the history, physical examination and laboratory findings, one may discern in the film "roentgenological equivalents" which may be present in kindred conditions in the same sense that the histological findings offer "morphological equivalents"

Case 16 Female—Age 46

A Negro female became ill on December 20 1953 with fever cough, dyspnea and painful swollen joints The patient was bed ridden at home for two weeks and treated with penicillin Although not fully recovered, she returned to work as a domestic On February 20, 1954 there was a return of fever, cough painful joints and at this time the patient also had chest pain and, on one occasion spat up a small amount of blood The patient was hospitalized on March 11, 1954 Examination revealed an acutely ill dyspneic woman temperature 103° F, pulse 110, respiration rate 24 blood pressure 100/80 Both hands, especially the left, showed fusiform tender swellings of the interphalangeal joints The right knee was also swollen and tender Examination of the chest revealed dullness over both sides and rales at the bases The heart revealed no abnormal findings The diagnosis was bilateral bronchopneumonia and rheumatoid arthritis, or,

possibly acute rheumatic fever and rheumatic pneumonia

Chest x rays revealed irregular patchy infiltrations throughout both lungs chiefly the left in keeping with an acute bronchopneumonia there was a pleural reaction at the bases (Figure 25A) The heart was not enlarged X rays of the hands showed fusiform swelling of the interphalangeal joints The joints themselves were not involved Laboratory tests revealed an accelerated erythrocyte sedimentation rate hemoglobin 79 per cent red blood cells 4 220 000 per cu mm white blood cells 8 700 per cu mm with a normal differential Urine was negative Mazzini was negative On a later occasion Mazzini + Wassermann ++ Serum albumin 3 2 mg per cent serum globulin 3 2 mg per cent on a later occasion the albumin was 2 6 mg per cent and the globulin 3 5 mg per cent electrocardiogram showed no abnormalities The patient was treated with combined antibiotics later with penicillin alone also salicylates and sedatives After one month penicillin treatment the patient developed a generalized rash which gradually subsided It was ascribed to penicillin sensitivity Although the chest x rays after three weeks showed considerable clearing of the lung fields the rales persisted The joint pains slowly abated the fever declined and the patient was discharged on April 24 1954

Six days later the patient was admitted to the Morrisania City Hospital because of recurrence of fever cough chest and joint pains The patient was acutely ill and dyspneic The rash was still present over the chest and upper arms The fingers toes and knees were swollen and painful on motion No abnormalities were found in the heart On auscultation numerous rales were heard in both lungs with a pleural friction rub at the right base Extensive laboratory studies were noninformative Chest x rays now revealed fine diffuse interstitial striations throughout both lungs especially the right and less of the pneumonic exudate seen in previous films pleural reaction at bases (Figures 25 B and C) The patient continued to have low grade fever Under salicylates the joint pains gradually subsided and the patient was discharged on May 26 1954

The patient as readmitted to the Morrisania City Hospital on July 1 1954 because of recurrence of pain in the hands wrists shoulders and ankles and swelling of the affected parts The patient was dyspneic and complained of a feeling of chest oppression Physical x ray and laboratory examinations revealed few changes from those noted previously On July 2 1954 a biopsy of the right lower lobe was done by Dr M Rubin The excised specimen was examined by Dr R Lubliner The lung was found somewhat firmer than normal but fairly well aerated the pleura slightly thickened Cut section revealed pinkish red parenchyma through which were scattered small strands of depressed grayish tissue Microscopic examination showed marked alteration of normal architecture foci of well aerated parenchyma alternating with foci of atelectasis There was thickening of interalveolar septa due to increased vascularity cellular infiltration and patchy fibrosis In many instances there was hyaline thickening of the walls of the small vessels within the septa The cellular infiltration was monocytic with a large number of plasma cells There was marked hyperplasia of the alveolar lining cells There was slight fibrous thickening of the pleura and of the interlobular septa There was moderate thickening of the interalveolar septa also in well aerated areas The diagnosis was interstitial and organizing pneumonitis with patch pulmonary fibrosis (Figure 25D)

The patient was treated with salicylates and sedation The joint pains gradually subsided She still had a low grade fever at the time of her discharge on July 23 1954 A chest x ray revealed a slight decrease in the pulmonary markings The pleural reaction was still present at both costophrenic sinuses In November 1954 the patient had a recurrence of painful swollen knees and ankles and she was admitted to the Bronx Municipal Hospital Center where she remained until May 23 1955

Laboratory examinations including repeated L E tests were unrevealing The patient was treated with various measures including butazolidin antibiotics salicylates and for about six weeks with cortisone There was a moderate degree of improvement in her rheumatoid symptoms The chest x rays also showed a temporary decrease in the degree of interstitial markings but not to a striking degree She is presently under observation in the clinic A chest x ray taken in November 1955 showed a considerable increase in the interstitial striations throughout both lungs The symptoms remained the same

Before concluding the discussion of the pulmonary lesions of rheumatoid disease it might be mentioned that the lesions are not unlike those encountered in rheumatic pneumonia described

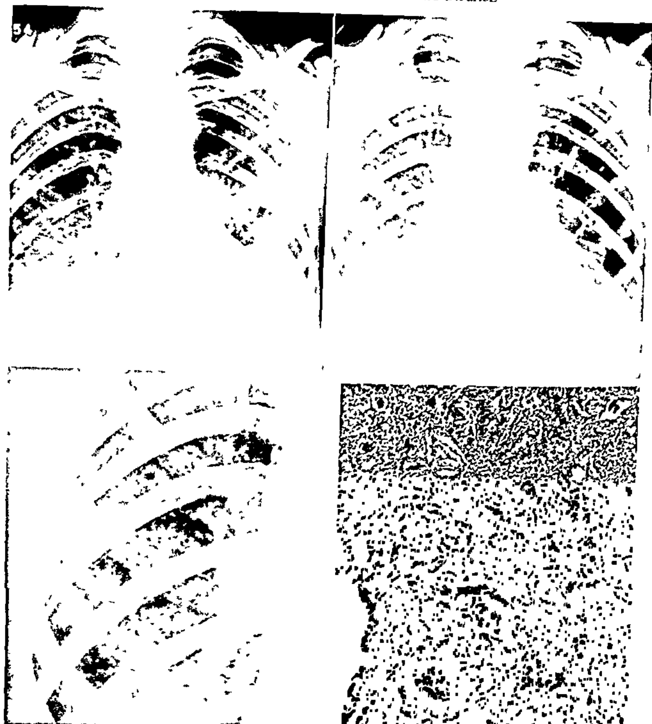


Figure 25 *Case 16* Rheumatoid disease with pulmonary lesions A (*Upper left*) Irregular, patchy infiltrations in both lungs, chiefly the left lower B (*Upper right*) Two months later, diffuse reticulations in both lungs, pleural reaction at bases C (*Lower left*) Lung detail showing fine striations D (*Lower right*) Lung (Biopsy specimen shows diffuse interstitial fibrosis, interalveolar septal thickening, hyaline thickening of walls of small blood vessels, exudate in alveoli) (From Rubin *Am J Med*, *19* 569, 1955)

in the preceding section It is also well known that the lung changes in rheumatic pneumonia and virus pneumonia have many features in common including the presence of a hyaline membrane mononuclear cell infiltration nonbacterial exudate, capillary engorgement and interstitial edema In fact rheumatic pneumonia may be mistaken for a virus infection and some believe that at least a small proportion of the latter are instances of rheumatic pneumonia Muirhead and Haley reported the case of a twenty five year old white woman who presented the concomitant occurrence of known healed inactive cardiac lesions and a peculiar interstitial pneumonitis The pneumonitis was widespread demonstrating a healed proliferative phase with extensive fibrosis and an active exudative phase In addition partly healed arterial lesions were observed in the lungs The authors point out that this case offered an additional point of interest in that the pulmonary lesions resembled in certain respects the changes described by Hamman and Rich in their cases of interstitial pulmonary fibrosis This brings up a rather intriguing subject which merits special consideration

The reason for including the Hamman Rich syndrome in the section on allergic diseases is because there is evidence that in some cases at least the condition is associated with hypersensitivity Furthermore the Hamman Rich syndrome enters into the differential diagnosis of many cases in which the chest x ray reveals diffuse interstitial pulmonary infiltrations For the present the discussion will limit itself to those forms of the Hamman Rich syndrome in which there is reason to believe that hypersensitivity plays an important role

Diffuse Interstitial Fibrosis of the Lungs Hamman Rich Syndrome

Since the introduction of the sulfonamides penicillin streptomycin and other specific antimicrobial agents the picture of the bacterial pneumonias has changed remarkably Not only has there been a precipitous decline in the incidence of lobar pneumonia and a comparative increase in the atypical forms but even the atypical forms are often bizarre One of these is a pneumonia characterized by diffuse interstitial fibrosis of the lungs This unusual disease was first brought to medical attention by Hamman and Rich in 1944 as an acutely progressive and fatal pneumonia But it soon became apparent that diffuse interstitial fibrosis of the lungs may be slowly progressive over a period of years There is reason to suspect however that many patients recover The frequency with which the latter takes place cannot be gauged accurately because the diagnosis rests on certain changes in the lungs which are demonstrable only at autopsy or by lung biopsy

A recent report by Wildberger and Barclay refers to thirty reported cases of the Hamman Rich syndrome This number gives an erroneous impression of the true incidence of the disease as it is currently being encountered This is borne out by the fact that of a collected series of 197 cases reported from only three sources in which lung biopsies were done for obscure pulmonary disease no less than sixty one showed interstitial or idiopathic pneumonitis with or without fibrosis and/or emphysema (see Table 11) Undoubtedly a considerable number of these represented instances of the Hamman Rich syndrome Dr Lubliner and I are presently studying a group of eighteen cases of the disease all proved by lung biopsy or autopsy or both observed at the Montefiore Hospital

Pathogenesis

The widespread use of antimicrobial agents may be one of the causes for the increasing incidence of atypical pneumonias of the type with which we are concerned at the moment Auerbach and co workers point out that solution of fibrin has long been held to be a function of enzymes derived from polymorphonuclear leukocytes Exudates which are rich in fibrin and poor in leukocytes are more apt to organize These investigators suggest that the widespread use of potent antimicrobial agents is contributing to a rising incidence of premature organization of pulmonary exudates with resulting fibrosis of lung tissue In this respect it should be noted

that an analogous situation is currently being encountered in pulmonary tuberculosis

Golden and Tullis also express the view that interstitial fibrosis may be on the basis of failure of resolution and subsequent organization following one or more attacks of acute interstitial pneumonitis ("primary atypical pneumonia") Geever and co-workers have shown that alveolar cells accumulate under various pathologic conditions, especially in pneumonias associated with virus infections, in which case the irritant factor is capable of producing septal cell proliferation and *actual lining The tendency to proliferation is* marked among the cells along the interlobular septa and, to a lesser degree, in perivascular and peribronchial areas These investigators draw attention to the fact that the inert lining may interfere with respiratory function Ogilvie and Hulse also suspect that the interstitial fibrosis is derived from the organization of the hyaline membrane which lines the alveoli during the acute stages of the disease

In their original communication, Hamman and Rich note that Winternitz had examined the specimens obtained from their patients with acute diffuse interstitial fibrosis of the lungs and found a striking resemblance to that found in the lungs of animals during experimental investigations on influenzal pneumonia The lung biopsy specimens of three patients with diffuse interstitial fibrosis associated with rheumatoid disease, referred to in the previous section as well as material of a larger group of patients with diffuse interstitial pulmonary fibrosis which Dr Ruth Lubliner and I have been studying for the past several years, were reviewed on various occasions by Zimmerman He also noted in the histology of many of the specimens features closely resembling those found in viral bronchopneumonia

An additional cause, or possibly an accessory factor, in the development of diffuse interstitial fibrosis of the lungs may lie in the allergic reactions which often accompany sulfonamide and penicillin treatment of atypical pneumonias Hamman and Rich drew attention in their publication to a group of cases of 'Current Bronchopneumonia of Unusual Character and Undetermined Etiology," which had been reported previously by Kneeland and Smetana, in which one of the cases corresponded clinically and anatomically with theirs In the *particular instance*, a woman of forty-seven developed urticaria simultaneously with chills and *blood streaked* sputum The patient was found to have progressive bronchopneumonia and was soon complicated by thrombophlebitis, anemia hypoproteinemia and right-sided heart failure leading to death At autopsy lesions were found in the pulmonary arteries suggestive of polyarteritis nodosa, in addition to diffuse interstitial pulmonary lesions characterized by a mononuclear cell exudate and a tendency to organzation also thickening of alveolar septa and narrowing of alveolar spaces The patient had received sulfapyridine and the vascular changes may have been related to the drug

Among the fifty two patients with atypical bronchopneumonia, described by Kneeland and Smetana, was a group of six "in whom the clinical picture of a severe and prolonged bronchopneumonia was complicated by a variety of phenomena suggesting that tissues other than pulmonary alone were involved Among these phenomena were migratory polyarthritis, erythematous skin eruptions, slight enlargement of the spleen and lymph glands, jaundice, gross hematuria, fibrinous pericarditis and encephalitis All six happened to be females and as these perplexing clinical panoramas unfolded themselves the notion kept recurring that there must be an associated element of diffuse vascular disease of the type seen in disseminated lupus or periarteritis nodosa"

It is difficult to determine to what degree the element of hypersensitivity plays a role in the Hamman Rich syndrome It is noteworthy, however, that there is a close similarity in the histological appearances of the pulmonary lesions found in this disease and in those encountered in rheumatic pneumonia, "rheumatoid disease' and the other collagen diseases Of particular significance is the fact that pulmonary lesions, apparently identical with those observed in acute interstitial pulmonary fibrosis, have been recently observed in patients with hypertension who are under prolonged treatment with hexamethonium

and hydralazine compounds The interstitial pneumonitis may progress quite rapidly in some cases Noteworthy, too is the fact that the so called hydralazine syndrome is associated with fever rheumatoid symptoms and in its severer forms with signs of acute disseminated lupus erythematosus including the occasional finding of L E cells Additional comments on this phenomenon a man made disease will be found in Chapter 12

As mentioned briefly in the section dealing with the pulmonary lesions in rheumatoid disease it appears that for one reason or another in some patients with systemic diseases of the types described in these pages the respiratory tract sustains the brunt of the damage while other organs are only slightly affected or even escape injury at least insofar as the latter can be recognized clinically This feature is forcefully brought to one s attention when a patient with a systemic disease including pulmonary lesions dies and the organs are examined at autopsy Excepting the lungs the other organs may show surprisingly little in the way of demonstrable tissue changes to indicate that the body had once been the seat of a widespread and profound disturbance Yet the clinical course of the disease may have been punctuated by a series of dramatic events affecting various parts of the body In this respect the clinician is occasionally in a more favorable position to evaluate the post mortem findings than the pathologist who not appreciating fully what had transpired during the patient s lifetime may find only fibrosis in the lungs an end stage of all manner of healed or partially healed disease With increasing use of lung biopsies performed relatively early in the course of systemic diseases which are accompanied by pulmonary lesions one is occasionally able to detect features in the lungs which indicate that the pulmonary involvement is part of a generalized disturbance although the exact nature of the latter is not always ascertainable

Clinical Features

Kahn Pecker and I described a typical case of diffuse interstitial fibrosis of the lungs and reviewed twelve cases reported to date (195?) Since then the literature on the subject has grown considerably Suffice it to state that the elements which influence the variability in the clinical picture may be related in part to the underlying cause in part to the severity of the disease in part to hypersensitivity of certain tissues to specific agents in part possibly also to the antimicrobial treatment and to factors still unknown If the fibrosis of the lungs is acutely progressive death may result from anoxia due to alveolar capillary block the thickened alveolar membrane preventing diffusion of gases (Austrian and co workers) If the disease evolves slowly over a number of years there is increasing obstruction of blood flow and hypertension of the lesser circulation leading to chronic cor pulmonale Clubbing of the fingers at times of a striking degree is often encountered In still others the lungs undergo diffuse hardening with focal emphysema and bronchiolectasis in a cystic lung similar to a type of cirrhotic organ encountered after the 1918 pandemic of influenza and now seen sporadically

It is impossible to judge how often diffuse interstitial disease of the lungs resolves without causing irreversible damage of the organs But this outcome probably occurs more often than is realized since the disease usually masks itself as an atypical or viral pneumonia The fact that the treatment with ACTH or cortisone of acutely progressive disease may be followed by dramatic improvement indicates that the disease may be reversible at certain stages in spite of the fact that roentgenologically the process appears to be well organized A word of caution is in order regarding the use of ACTH or cortisone in the treatment of the disease Peabody and co workers also Schechter and others warn against the sudden withdrawal of the steroids once begun lest an acute and possibly fatal rebound reaction occurs Once initiated steroid treatment has to be continued indefinitely and discontinued very slowly if one is forced to do so

With respect to the possible role which hypersensitivity may play in causing diffuse interstitial fibrosis of the lungs the case histories of the following two sisters are most instructive A somewhat analagous experience was documented



Figure 26 *Case 17* Interstitial pulmonary fibrosis of probably allergic etiology, in sisters A (*Left*) Diffuse reticulations in both lungs more marked in upper lobes B (*Right*) Three years later marked increase in interstitial infiltrations with minute areas of honeycombing in upper lobes (Death one year later caused by respiratory failure Autopsy disclosed scattered small air cysts interstitial fibrosis diffuse emphysema and bronchopneumonia See *Case 18*)

by Peabody and co workers in the case of identical twin sisters At the time of the report by these authors the findings had been confirmed at autopsy in one of the sisters Later MacMillan reported that the surviving sister had also died and had revealed at autopsy lung findings identical with those of the twin MacMillan s communication dealt with familial pulmonary fibrosis Wildberger and Barclay also reported the finding of diffuse interstitial pulmonary fibrosis in siblings in whom the disease had been evolving over a period of approximately ten years The occurrence of a comparatively infrequent disease in members of the same family speaks for a genetic factor In the following case reports of two sisters hypersensitivity may have played a role

Case 17 Female—Age 40

The patient s illness began in 1946 with cough productive of mucoid and bloody sputum also exertional dyspnea orthopnea and weight loss A chest x ray taken at a Board of Health Clinic revealed minimal fibrosis in both lungs By the end of 1948 the pulmonary infiltrations became much more noticeable The sputum being negative for tubercle bacilli a provisional diagnosis of sarcoidosis was made Of interest in the patient s past and family histories was the fact that she had a severe form of dermatitis which took many years to clear up The patient s sister whose case history will be cited shortly had hay fever and was allergic to drugs especially aspirin which caused the skin to swell and itch Several other members of the family had hay fever

In the Spring of 1949 the patient was admitted to the Department of Internal Medicine of the University Hospital Michigan and the following notes of the case record were kindly supplied The patient was a thin pale white female who appeared to be chronically ill The only positive findings on physical examination were the presence of clubbed fingers and toes and rales at the lung bases Various laboratory tests were done but the findings were within normal limits The chest x ray showed widespread granular coalescing lesions in both lungs Bronchoscopic examination showed a normal tracheobronchial tree Sarcoidosis was suspected At the time of the patient s last examination

at the University Hospital she was quite upset, complaining of cough insomnia and dyspnea

I examined the patient for the first time on September 30 1949 The patient weighed 70 lbs She had excessive cough expectoration and dyspnea. Chest x rays revealed diffuse interstitial fibrosis of both lungs with innumerable cystic spaces throughout both organs (Figure 26) Because of increasing symptoms the patient was admitted to Fordham Hospital where she required constant oxygen administration because of her respiratory distress The patient's condition steadily worsened and she died on July 13 1950 approximately four years from the time of onset of symptoms

At autopsy the major findings were limited to the thoracic organs The heart weighed 320 grams There was mild calcification of the tricuspid and mitral valves There was no evidence of arteriosclerotic changes in the coronary vessels or aorta No adherent thrombi were found in the heart chambers The surfaces of both lungs were covered by emphysematous blebs about the size of marbles The blebs contained no fluid or exudate The lower lobes were dark purple in color and of a liver-like consistency On cut section the lungs revealed a most inelastic tissue with small air cysts scattered throughout the parenchyma Microscopic examination showed extensive pulmonary fibrosis causing destruction of lung parenchyma There were large, irregular patches of fibrosis with a few scattered entrapped alveolar spaces distended and lined by hyperplastic cuboidal cells Adjacent to scars were patches of emphysema alternating with patches of atelectasis The latter showded fibrous thickening of interalveolar septa no inflammatory cell infiltration There was moderate thickening of vessel walls secondary to the fibrosis The anatomical diagnosis was diffuse chronic cystic disease and interstitial fibrosis, diffuse emphysema, bronchopneumonia

Case 18 Female—Age 58

The patient became ill late in 1948 with cough, expectoration and dyspnea Except for the presence of rales at the lung bases the physical examination by her physician revealed no significant abnormalities A chest x ray showed diffuse fibrosis of both lungs A Mantoux test was negative The sputum was negative for acid fast organisms The patient's symptoms slowly increased At this time a bronchoscopy was done and no abnormalities were found No glands presented themselves



Figure 27 *Case 18* Interstitial pulmonary fibrosis of probably allergic origin in sisters A (*Left*) Diffuse reticulations throughout both lungs B (*Right*) Lung Diffuse fibrosis and honeycombing (Histologic examination showed marked thickening of interalveolar septa increased vascularity and mononuclear cell infiltration hyperplasia of alveolar lining cells patches of interstitial fibrosis and foci of recent bronchopneumonia (See *Case 17*)

for biopsy It was the impression of the attending physician that the patient had sarcoidosis or a non specific pulmonary fibrosis of undetermined etiology A chest x ray taken in August, 1950 revealed no significant changes from those noted a year previously (Figure 27A)

Of additional interest in the patient's history was the fact that she had a salpingectomy and oophorectomy and had received radiotherapy five years previously The patient stated that for many years she had been having hay fever and as a young woman had suffered of an allergic dermatitis The patient's sister whose history was cited previously also suffered of allergies as did several other members of the family The patient managed to be up and about until the middle of 1951 when she was forced to spend increasingly more time in a chair and later in bed because of dyspnea and recurring febrile episodes

I examined the patient for the first time on September 15 1951 when she was admitted to a hospital in acute respiratory distress which was only partially relieved by oxygen Examination revealed a gray haired small shrunken woman of about 70 or 80 lbs in weight who appeared considerably older than her stated age The percussion note was resonant over both sides of the chest except in the left axilla On auscultation very few rales were heard on the right side but rhonchi were heard in the left and moist rales at both bases The heart rate was rapid no murmurs were heard The abdomen was flaccid the liver was palpable but did not seem enlarged There was no edema of the extremities A bedside chest x ray taken the day previously revealed mottled infiltrations throughout both lungs and a conglomerate mass of consolidation apparently a pneumonia at the left base The patient's course was rapidly downhill and she died the same night The postmortem examination done under difficulties was limited to the lungs, heart, a piece of liver, spleen and the left kidney

The lungs revealed nodularity of the pleural surface On section there was diffuse honeycombing of the organs (Figure 27B) Histological examination showed all variations from early to advanced pulmonary fibrosis and foci of recent bronchopneumonia and purulent bronchitis Sections revealed alternating foci of emphysema and atelectasis slight thickening of walls of medium size blood vessels Other sections revealed marked thickening of interalveolar septa increased vascularity and mononuclear cell infiltration, alveolar spaces distorted, elongated often distended also hyperplasia of alveolar lining cells Still other sections revealed large patches of interstitial fibrosis in places still fairly cellular, the remaining alveolar spaces distended filled with edema fluid and alveolar macrophages also foci of bronchopneumonia organizing pneumonia and interstitial pneumonitis

In conclusion it may be stated that diffuse interstitial fibrosis of the lungs is probably the end result of a variety of agents In most instances the cause cannot be determined Occasionally it is possible to pin a label on the disease if, for example, it occurs in association with sarcoidosis, beryllIosis or some other granulomatous condition, or is due to a recognizable viral or bacterial pneumonia There is also a group where there is reason to suspect that the lesions in the lungs represent the pulmonary manifestations of a hyperergic state, the term used in its broadest sense to include rheumatic pneumonia rheumatoid arthritis, scleroderma, disseminated *lupus erythematosus*, and possibly other conditions

Bibliography

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Chapter 7

Diseases of the Skin and Mucous Membranes

Introduction

IT IS A MATTER of common knowledge that metabolic, allergic, infectious and malignant diseases of internal organs may affect the skin Less widely known is the fact that there are a sizable number of diseases with predominant localization in the skin and mucous membranes which also find expression in deeper organs and tissues of the body *Of particular interest, from* the viewpoint of the present discussion, are the pulmonary manifestations appearing at the inception of certain skin diseases with every indication that the changes in the lungs represent an integral part of a systemic disease As a rule, little attention is paid to the pulmonary findings in skin diseases unless the former are pronounced Either no abnormal signs are elicited on physical exploration of the chest or else the condition of the skin may be in a state as to preclude a *thorough examination At best the pulmonary* involvement is recognized only when a complicating pneumonia supervenes or is a terminal event in the course of a chronic debilitating illness

In the usual type of skin disease, encountered in office and clinic practice a chest x ray is seldom considered necessary and as a result much important information which might be obtained by this means does not come to light Yet, there is evidence that even in apparently superficial skin diseases the internal organs may be implicated Discerning dermatologists have for years stressed the fact *that few skin diseases are* skin deep Physicians have long been aware of the fact that the skin is a sensitive barometer in *health and disease and often serves as a mirror* of disease of internal organs Of late, increasing interest is also being directed to the reverse of the image the lungs as a mirror of skin disease

As a point of historical interest, Keil draws attention to the fact that Osler, as early as 1888 and in later communications, suggested that in certain systemic diseases notably the erythema group, alterations occurring in the skin have their counterpart in internal organs In some, the visceral manifestations precede the cutaneous ones *A classical example of this interrelationship,* and with which Osler s name is associated is hereditary hemorrhagic telangiectasis We have learned since that systemic lupus erythematosus sarcoidosis and several other conditions to be described later, which were at one time considered dermatologic disorders may, in fact, never reveal themselves in the skin during the entire course of the disease

Allergic Dermatitis

Fleeting pulmonary infiltrations associated with eosinophilia may punctuate the course of acute and chronic allergic diseases involving the skin The dermatologist seldom gives *thought* to the lungs unless there is a complicating pneumonia, the physician interested in chest diseases is unlikely to have an opportunity to see such patients because, as a rule, there are no symptoms or signs referable to the lungs, and the roentgenologist, knowing little of the patient's history *and dermal condition* is apt to be at a loss to explain the abnormal roentgen findings as illustrated by the following experience

An elderly *man had been convalescing* from

an acute pneumonia. Repeated chest x-rays during the illness had shown progressive resolution of the process. Shortly before the patient was scheduled for discharge, a chest x-ray was taken to make certain the lungs were clear. The patient's physician was hurriedly called by a disturbed roentgenologist and told that the film revealed pulmonary infiltrations, probably representing miliary tuberculosis. When I saw the patient, the latter was up and about feeling quite well but complaining of itching of the skin which was associated with an erythematous rash of the face, chest and upper extremities. The condition was obviously a late hypersensitivity reaction to the penicillin which the patient had been receiving. The finding of eosinophilia in the blood and the rapid disappearance of the pulmonary infiltrations, coincidentally with the subsidence of the skin eruption, confirmed this belief.

On another occasion, I had occasion to see a young woman of twenty-one who had been under treatment for a severe form of neurodermatitis and seborrheic dermatitis. Patch tests revealed positive reactions to various contactants. Repeated chest x-rays had failed to reveal any abnormalities. Several blood examinations had shown nothing unusual, the eosinophil count averaging 1 per cent. On one occasion the patient developed fever and chest pain. A chest x-ray revealed irregular infiltrations in the lower portions of both lungs and accentuation of the hilar markings. Blood counts at this time showed a moderate leukocytosis with 10 per cent eosinophils, subsequent counts revealed an eosinophilia as high as 16 per cent. The sputum also contained eosinophils but no acid fast organisms. The infiltrations disappeared gradually and the lungs resumed their previous state.

Frostberg relates the case of a twenty-six year old woman who was treating herself with mercury ointment for scabies. The patient developed an acute dermatitis with fever, rapid pulse and leukocytosis, no eosinophilia. Chest x-rays disclosed reticular markings in both lower lung fields. With the fading of the exanthem, the roentgenogram resumed its original configuration. Prompted by this experience, Frostberg had routine chest x-rays taken of all patients with acute generalized dermatitis where "the clinical findings were of such a nature that lung involvement might be suspected." In less than a year, Frostberg encountered a man of forty with an intense dermatitis, probably due to barbiturate medication. The chest x-ray revealed mottled and reticular densities. In addition, there was an eosinophilia of 12 per cent. The infiltrations cleared with the disappearance of the exanthem. As in the first case, there were no clinical signs referable to the respiratory tract. The roentgen findings were ascribed in both instances to a hypersensitivity reaction in the lungs of a type seen in Loeffler's syndrome. Two similar experiences were reported by Falk and Newcomer. The cause of the fleeting pulmonary infiltrations in their cases was believed to lie in an allergenic penicillin-oil wax preparation which was being administered for early syphilis.

Reference was made in Chapter 5 to, so-called, "creeping eruption" of the skin, endemic in the Southeastern coastal regions of the United States, which may be associated with Loeffler's syndrome. In 1917, Kirby Smith suggested a nematodal origin of the disease and, in 1926, with Dove and White, proved this to be the case. Wright and Gold were the first to describe the association of cutaneous helminthiasis with Loeffler's syndrome. It appears that the infection with the filariform larvae of the *Anclystoma braziliense* (hookworm of dogs and cats) occurs most frequently on beaches and under houses. The disease is therefore apt to be contracted by swimmers, children, painters, carpenters and termite exterminators. The larval form of the nematode, when it comes in contact with the skin, loses its cutaneous sheath and penetrates the skin. A small papule develops at the site of penetration and soon serpiginous, elevated burrows appear, the urticarial like lesion being associated with considerable itching. Wright and Gold were unable to find *Anclystoma* ova in a single instance of 441 stool examinations made in a series of seventy-six cases. Nevertheless, Loeffler's syndrome was encountered in twenty-six. These investigators therefore concluded that the pulmonary infiltrations were caused by an antigenic response to the presence

of either the larvae or the blood borne exotoxin However, the possibility of the pulmonary infiltrations being caused by transpulmonary larval migration cannot be excluded

Erythema Multiforme

This disease is characterized by pleomorphic changes in the skin, chiefly of the extensor surfaces of the limbs consisting of erythema, papules and/or vesicles and bullae The seasonal incidence and, at times, epidemic occurrence of the disease, the febrile systemic manifestations, the mononuclear and nonbacterial character of the exudate, and the simultaneous development in some cases of atypical pneumonia, point to a generalized inflammation If the disease is caused by a single agent, it is most likely due to a virus Finland and co-workers obtained positive complement fixation tests for psittacosis in two cases and a positive cold agglutination test in one Increasing numbers of investigators are subscribing to the belief that the disease, at least in some patients, is of allergic nature caused by hypersensitivity to drugs or bacterial or viral products A feature of one form of erythema multiforme is the occurrence of stomatitis, conjunctivitis and balanitis, occasionally in association with pneumonia This syndrome is variously described as "eruptive fever," 'mucosal respiratory syndrome," 'Stevens-Johnson syndrome" and by several other eponyms

Keil was among the first to draw attention to the fact that erythema multiforme may be associated with simultaneous involvement of the trachea, bronchi and lungs In fact Hebra who coined the term 'erythema multiforme exsudativum,' referred in his classic *Diseases of the Skin* published in 1866, to a case complicated by pneumonia The prominence of the respiratory tract involvement and the integral part which this system plays in erythema multiforme is stressed in a publication by the Commission on Acute Respiratory Diseases created during World War II The report includes case histories of six patients, three of whom had atypical nonbacterial pneumonias Finland and co workers reported six cases of erythema multiforme associated with pneumonia Stanyon and Warner observed seventeen military personnel with striking skin and mucosal lesions, fourteen of whom had pulmonary involvement at sometime during the course of the disease

The onset of the disease is usually abrupt following a short prodromal period In many the onset is ushered in by an upper respiratory infection with fever, malaise, sore throat, cough and other symptoms commonly encountered in influenza In an analysis of twenty patients personally observed, and twenty two collected from the literature, Soll found twenty nine (69 per cent) to have had prodromal respiratory symptoms The malignant form of erythema multiforme as noted by Costello, is particularly apt to be associated with pneumonia At the height of the disease, pain in the eyes, photophobia, difficulty in swallowing, high fever, cough dehydration and prostration may reach alarming proportions In the majority there is rapid clearance, in some, the disease pursues a fatal course

Pneumonia occurring in association with erythema multiforme closely resembles that seen in the primary atypical variety An unusually instructive case was presented by Markham at a clinical meeting of the Kingston Garrison Medical Society The particular patient developed signs and symptoms of what seemed to be an atypical pneumonia Shortly after the onset of the disease there appeared a severe conjunctivitis a membranous eruption of the mucous membranes of the mouth, a bullous skin eruption and balanitis Several other cases have been described in which the pneumonia and skin manifestations appeared simultaneously But, in view of the fact that in some of the cases there were no antecedent x-rays of the chest available, the pulmonary involvement may have been present but was unrecognized before the eruptive changes in the skin took place

The pulmonary findings in patients with erythema multiforme are best appreciated in serial chest x-rays taken during the course of the disease In the majority, one encounters a simple bronchitis in association with the acute mucosal lesions of the mouth, larynx and pharynx with-

out demonstrable involvement of the lungs In others the chest x rays reveal changes in the lungs consisting either of (1) miliary or nodular densities simulating tuberculosis (2) scattered patchy infiltrations in one or both lungs such as one encounters in bronchopneumonia (3) massive pneumonic consolidations and (4) on rare occasions a complicating pleural effusion The postmortem findings as might be expected represent a summation of tissue changes caused by superimposed infection in association with acute congestion and suppuration

Since treatment of pneumonia with sulfonamides and other drugs may cause skin eruptions one has to be on guard when using such drugs not to confuse toxic skin reactions with erythema multiforme In any event sulfonamides penicillin and aureomycin have little effect on the disease itself although they do help control secondary infection Yates and co workers also Agostas and co workers obtained favorable immediate results with ACTH and cortisone treatment Since most cases recover without treatment one has to maintain a critical attitude of the value of therapeutic agents However further exploration with the use of ACTH and cortisone is indicated

Erythema Nodosum

According to Beerman erythema nodosum is an example of the intangible borderline between dermatology and internal medicine Erythema nodosum is a self limited disease of a few weeks duration The skin lesions are characterized by the appearance of discrete red tender nodules of varying size in the subcutaneous tissues especially of the forearms and legs The nodules may appear in crops The eruption is often preceded by a febrile episode sometimes chill also sore throat joint pains and constitutional symptoms After the subsidence of the acute stage the nodules gradually change in appearance to a dark red then a livid color a yellowish pigmentation persisting in the skin for sometime after the disappearance of the lesions Histologically the nodules are composed of fibrinoid degeneration of connective tissue septa granulomatous foci of histiocytes and lymphocytes with occasional giant cells of the foreign body type

The cause of erythema nodosum has been a subject of discussion for many years Earlier observers considered the condition a specific disease a belief which persisted until quite recently The hypothesis of the specificity of erythema nodosum became less tenable as increasing numbers of conditions were found associated with a similar skin eruption In a significant percentage of cases especially in the Scandinavian countries and in England erythema nodosum has been found in association with recent tuberculous infections Of late the view is receiving increasing support that erythema nodosum is a nonspecific allergic reaction to a variety of bacterial chemical and toxic agents Special attention has been directed to infections associated with B hemolyticus streptococci coccidioidomycosis and sulfonamide medication Lofgren and Wahlgren concluded from a study of sixty four cases that the histological picture is in keeping with an allergic skin eruption With increasing use of routine chest roentgenography large numbers of cases are found without any associated diseases

The intrathoracic manifestations of erythema nodosum concern chiefly often exclusively the hilar lymph nodes However the lung parenchyma may be involved without noteworthy participation of the lymph nodes In children there is apt to be a unilateral density extending fanwise from the hilus into the adjacent parenchyma (Figure 28A) In adults the hilar tumefactions are larger usually bilateral and the lung parenchyma is more likely to be involved (Figure 28B) Of particular interest from the viewpoint of differential diagnosis is the striking resemblance roentgenologically of erythema nodosum and sarcoidosis In fact Kerley found that approximately 25 per cent of the patients with sarcoidosis had a history suggestive of erythema nodosum It might be mentioned that many investigators make no distinction between the two conditions and ascribe both to manifestations of hypersensitivity

Lofgren in Scandinavia found pulmonary



Figure 28 Erythema nodosum with intrathoracic lesions A (*Left*) Prominent hilar densities, more marked on left (in a boy of ten years) B (*Right*) Bilateral, prominent hilar densities (in a man of twenty one years)

changes of fresh appearance, at the first roentgenographic examination *after the skin eruption,* in 78 per cent of 178 cases of erythema nodosum The incidence of unilateral glandular enlargement showed a direct relationship to the degree of tuberculin sensitivity but in the presence of bilateral hilar lymph node involvement the reverse was true In the presence of bilateral hilar lymph adenopathy, a considerable number were found to represent sarcoidosis Johnson and his co workers believe that if evidence of hilar adeno pathy is found in the chest x ray of a case of erythema nodosum the hilar enlargement is simply part of a disease of nonspecific etiology It is a common experience for one to find accidentally in chest x-rays bilateral hilar lymph node enlargement and in many instances a cause cannot be found By 'rule-of thumb,' unilateral hilar lymph node enlargements in children with *positive tuberculin skin tests is assumed to be* caused by tuberculosis, bilateral lymph node enlargement with negative tuberculin skin tests in adults is assumed to be sarcoidosis.

Hodgson and co workers list the following conditions which may be associated with bilateral hilar adenopathy (1) tuberculosis, (2) BCG vaccination, (3) infections histoplasmosis and coccidioidomycosis, (4) sarcoidosis, (5) pneumoconiosis, (6) lymphogranuloma venereum, (7) secondary syphilis (8) neoplasms Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, giant follicular lymphoma and leukemia, (9) metastatic malignant growths of the lung and elsewhere, (10) conditions associated with erythema nodosum and (11) fibrocystic disease of the pancreas

Disseminated Lupus Erythematosus

Introduction

'Lupus erythematosus, erythema nodosum and sarcoidosis, all diseases which historically were dermatologic conditions have, with the advances in diagnosis become important entities which are the concern of all diagnosticians' (Michaelson) In fact, as increasing numbers of patients with systemic lupus erythematosus are being recognized, internists are gradually usurping this intriguing disease from dermatologists and adopting it as their own The L E test, now widely used in diagnosis, as well as the recent introduction of cortisone and corticotropic hormonal treatment, have served to popularize the disease among phy-

sicians at large Disseminated lupus erythematosus, at one time considered a rarity, is now being diagnosed with considerable frequency Du Bois reported that in the years 1948 and 1949 the diagnosis was made eleven times in the Los Angeles General County Hospital But after the hospital staff became "lupus conscious," a total of forty four cases were diagnosed in the following two years

The systemic manifestations of lupus erythematosus were described by Kaposi in 1872 and by Jadassohn early in the present century It is more likely, however, as suggested by Klemperer, that the observations of these investigators referred primarily to the toxic symptoms of the cutaneous involvement Older dermatologists recognized a localized, discoid form now believed to be only one of the manifestations of the disease Keil is largely responsible for dissociating lupus erythematosus from tuberculosis a belief once widely held as attested by the name which bears no relation to the true nature of the disease Keil also pioneered in the concept that a number of skin diseases including disseminated lupus erythematosus, are only outward manifestations of more profound disturbances affecting deeper organs and tissues of the body

Clinical Features

Disseminated lupus erythematosus affects chiefly females, especially those of the second and third decades of life Red haired young women with a tendency to freckling of the skin are especially vulnerable The appearance of the skin is characterized by a butterfly erythema on the bridge of the nose and cheeks which is sensitive to light drugs and irritants of any type Older lesions may show atrophy, telangiectasis and pigmentation but some doubt that these changes are in reality lesions of disseminated disease Aberrant forms are not uncommon Cutaneous lesions may be absent or they may appear late in the disease

Systemic involvement is associated with fever, joint manifestations of varying severity lymph node enlargement and a prolonged remissive course The disease is almost invariably fatal however, individual cases have been reported where the disease had lasted twenty years and longer The endocardium, kidneys bone marrow and serous membranes are often implicated producing their own train of symptoms and signs Laboratory procedures of value in diagnosis include a leukopenia with a uniform reduction of all the white cells a rapid blood sedimentation an inversion of the albumin globulin ratio the hyperglobulinemia being made up chiefly of the gamma fraction The latter is believed to cause an occasional false positive serological reaction for syphilis, a phenomenon in itself of diagnostic significance

The presence of inclusion bodies, so called "L E cells," in the peripheral blood and bone marrow is invaluable as a diagnostic aid The important work leading to the discovery of the test was begun by Hargraves and developed further by Haserick and others The "L E cell" is a polymorphonuclear leukocyte which contains a mass of ingested nuclear material and gives staining reactions identical with those of the haemotoxylin staining bodies found in the viscera Klemperer and co workers identified the material as depolymerized desoxyribosenucleic acid and related it structurally to the inclusion bodies of the L E cell Hargraves correlates the L E phenomenon with blood coagulation, especially the blood platelets and their disintegration products L E inclusion bodies in disseminated lupus erythematosus may be demonstrated in sternal marrow as well as in peripheral blood Haserick obtained positive L E tests in twenty-two patients fifteen of whom had no skin eruption at the time of the positive test, six of these developed later a typical erythema

The L E phenomenon has been claimed by some to be pathognomonic of the disease However, cases have been reported in which L E cells have been found in dermatitis herpetiformis diffuse interstitial fibrosis of unknown cause, in an appreciable number of rheumatoid arthritis, polyarteritis nodosa, miliary tuberculosis during cortisone withdrawal, hydralazine toxicity, scleroderma leukemia, pernicious anemia in relapse and multiple myeloma A significant number of false positive tests have been reported in association with severe hypersensitivity reactions to

penicillin According to Cohen, this may provide a link between this disease and polyarteritis nodosa whose relationship to drug sensitivity is well established The occurrence of L E cells in association with hypersensitivity is suggestive that the phenomenon may be related to an immunologic mechanism In this respect it might be mentioned that the reported finding of L E cells in some cases of pleural effusions of undetermined etiology is also in keeping with hypersensitivity It should be noted that not infrequently a pleural effusion heralds the appearance of disseminated lupus erythematosus In general, the specificity of the L E phenomenon in acute disseminated lupus erythematosus, is of such high high order that it is good practice to utilize the test routinely in every unexplained febrile or undiagnosed systemic disease The L E test is also of considerable prognostic value because it permits the evaluation of results of treatment as well as being a useful tool in studying the mechanism of the disease It should be noted, however, that if careful search is made L E cells are usually found in patients under most effective steroid treatment Apparently the basic disturbance is not greatly altered by medication

Pathology

The pathological changes in disseminated lupus erythematosus are essentially of a two fold *nature (1) those referable to vascular involvement*, and (2) those referable to fibrinoid degeneration of connective tissue The involvement of blood vessels interferes with fluid interchange and affects not only the systemic circulation but also, at times the pulmonary circulation The vascular changes may consist of simple dilatation of the capillary bed or proliferative lesions of the lining epithelium of the capillaries, arterioles and venules The changes are often associated with thrombi and occasionally occlusion of vessels, there are also degenerative and necrotizing lesions Fibrinoid degeneration of the connective tissues of the mesenchymal organs results in fragmentation of these elements, swelling and increased density of the interfibrillar ground substance, eventually *resulting in sclerosis*. These features are shared to variable degrees by polyarteritis nodosa, vasculitis of rheumatic fever, scleroderma, dermatomyositis and several others of, the so called collagen group of diseases

Pulmonary Lesions

The pleuropulmonary manifestations of systemic lupus erythematosus have received little attention possibly because the lungs do not show as striking features of the disease as do the heart, kidneys, joints and hemopoietic organs Yet, there is hardly a patient with acute systemic lupus erythematosus who does not have, at one time or another, involvement of the lungs especially of the pleura The pleural involvement may be recurrent affecting one cavity or the other It may be of a dry fibrinous variety or appear as an effusion of moderate or massive proportions Tumulty found that if the effusion is massive it may herald secondary infection He also found tuberculosis not an uncommon complication Suppurative bronchopneumonia is also frequently encountered

In occasional instances one meets with patients who have recurrent unexplained respiratory tract infections, with or without gross evidence of pneumonia, long before the true nature of the disease becomes clinically apparent There is every reason to expect that a disseminated disease, such as lupus erythematosus, with a predilection for vascular structures, connective tissue and serous membranes, should find the lungs and pleura favorable sites for development In a study of 105 patients with systemic lupus erythematosus, Tumulty was impressed with the frequency and importance of the pulmonary involvement This investigator observed two types of alterations those due to the lupus itself and those due to secondary bacterial infection The involvement of the lung by lupus, according to Tumulty, is often overlooked or considered to be a pneumonia of bacterial or viral origin The basilar portions of the lungs are most vulnerable, a prominent feature being connective tissue organization of alveolar spaces resulting in small patches of atelectasis

The symptoms and signs of pleuropulmonary involvement in systemic lupus erythematosus in-

clude cough chest pain dyspnea bloody sputum and gross hemoptysis The bloodspitting may be due to the acute arteritis of the pulmonary blood vessels or to cavitation resulting from anemic necrosis of affected lung tissue A pleural friction rub is often heard and there is early appearance of fluid in the pleural cavity often on both sides Occasionally the fluid is hemorrhagic the blood probably originating in petechiae of the pleural cavity Jessar and co workers analyzed the symptomatology of a collected group of 279 patients with disseminated lupus erythematosus during the years 1948 to 1953 They found in their own cases manifest pleural effusion in 39 per cent pleural rub in 20 per cent and pneumonitis in 20 per cent In the collected series, symptoms or signs referable to the respiratory tract were recorded in 38 per cent including pleural effusion in 29 per cent The authors draw attention to a fact one which is often overlocked that in any given group of patients approximately 20 per cent will be alive at periods greater than five years from the onset of the disease

In an analysis of eighteen autopsied cases of disseminated lupus erythematosus including one of their own the Reifensteins found pleuritis with or without effusion a constant feature They noted that it was common for signs of pulmonary involvement to be present for many months during the course of the disease Thirteen of the eighteen cases had pulmonary consolidation and an additional four congestion or partial collapse of the lungs In most instances the consolidation was of a patchy nature in a few it was lobar Griffith and Vural in a similar study of eighteen autopsied cases found abnormalities in the lungs and pleura in every one

Purnell and co-workers studied the pulmonary lesions of lupus erythematosus in fifty four patients examined at autopsy In more than half bronchopneumonia hemorrhage pleural effusion edema interstitial pneumonia or congestion often a combination were demonstrable Likewise Klemperer Pollack and Baehr in a study of the autopsy findings in twenty cases noted that the postmortem changes do not properly reflect the remarkable clinical manifestations of the pulmonary involvement in this disease—the long bouts of waxing and waning migrating bronchopneumonia These investigators draw attention to the serous membrane involvement in this disease which is characterized by strikingly thick gelatinous and succulent tissue Humphreys was likewise impressed by the loose gelatinous fibrous adhesions often seen in the pleural spaces of patients with systemic lupus erythematosus

Particularly instructive from the viewpoint of pleuropulmonary involvement are reports of individual patients followed for long periods Rakov and Taylor reported an instance of systemic lupus erythematosus in which the dominant feature of the disease was a long continued consolidation of the lungs which appeared early in the course of the disease and persisted for eight months until death The authors considered the pulmonary involvement an integral part of the disease The postmortem examination revealed lobular consolidation with intervening air containing alveoli surrounded by thickened alveolar septums also a low grade chronic inflammation consisting almost entirely of large mononuclear cells The greatly thickened pleural surface of the lung was made up of fibrous tissue which was highly vascular and still the seat of a fairly intense inflammation also consisting almost entirely of mononuclear elements

Baggenstoss noted in his cases a peculiar basophilic mucinous edema in the connective tissue of the alveolar walls and in the peribronchial and perivascular tissues This finding was noted in nine of fifty four patients examined at autopsy and usually in association with interstitial pneumonitis and alveolar hemorrhage The mucinous interstitial edema was believed to be the precursor of the interstitial pneumonitis Cluxton described a case of systemic lupus erythematosus in which the alveolar walls of the lungs presented a picture not unlike the appearance of the so called wire loop lesions found in the kidneys Others have called special attention to the acute arteritic changes of the pulmonary blood vessels

ROENTGENOLOGY

The roentgen findings of systemic lupus erythematosus, with reference to the pleuropulmonary involvement, are in keeping with the pathological process. Although abnormal changes are encountered, they are not characteristic of the disease. However, the changes assume added importance if the nature of the systemic disease is known or suspected (Figure 29). If experience with other collagen diseases can serve as a guide, it is very likely that once the significance of the roentgenological changes is fully appreciated, the chest x ray will also serve as an aid in the diagnosis of obscure disease. Tumulty ascribes particular significance to patchy atelectatic areas in the basal portions of the lungs and the resulting elevation of the diaphragm. In the fifty four autopsied cases, reported by Purnell and co-workers, focal or diffuse atelectasis was found in 44.3 per cent. A case is reported by Ellman and Cudkowitz of a young woman who became ill with an acute febrile disease characterized by cyanosis and dyspnea. A shadow at the right base was regarded as being due to a subphrenic abscess but at operation no pus was found. Later a diffuse opacity was seen at the right base as well as mottling at the left lower lobe. The left subphrenic space was then explored surgically and again no pus was found. Three months later an erythema appeared on the face and the diagnosis of lupus erythematosus was no longer in doubt.

Israel reported twenty eight patients with established diagnosis of disseminated lupus erythematosus, in nine, confirmed at autopsy. Roentgen or pathologic evidence of pulmonary involvement was found in twenty of the twenty-two patients. Fifteen patients showed, on one or more admissions, clinical and roentgen evidence of pneumonia, in two, previously unsuspected pneumonias were found at autopsy. Two patients had pleurisy with large effusions and one patient had diffuse perivascular or vascular changes. Israel was able to differentiate three groups of cases with varying pulmonary patterns. One form was characterized by recurrent pneumonia, a second showed lesions simulating tuberculosis, and a third had predominantly respiratory symptoms.

Bille, also Thorell, direct attention to the pleural and subpleural changes. In a study of five cases there were pleural changes noted in the chest x-rays consisting of pleural thickening, small effusions and subpleural changes in the adjacent parenchyma best demonstrated in oblique projections. The frequency of pleural involvement is brought out in the study of Purnell and co workers. No less than two-thirds of the patients had pleural effusions. It was bilateral in 48.1 per cent and unilateral in 18.5 per cent. Unexplained pleural effusions, especially if bilateral, occurring in women in whom there may be reason to suspect a systemic disturbance, should bring to mind the possible presence of disseminated lupus erythematosus. Small pleural effusions are often associated with oblique or horizontal striations, the exact nature of which is problematic (Figure 30B).

In patients in whom the disease pursues a more chronic course, one may encounter chest x-ray findings in keeping with a diffuse interstitial fibrosis associated with small pleural effusions, very much like the changes seen in other collagen diseases. The following case illustrates the "classical" features of disseminated lupus erythematosus, including the pleuropulmonary changes.

Case 19 Female—Age 19

A white girl was admitted to the Morrisania City Hospital July 5, 1950 complaining of joint pains, weakness and loss of twenty five pounds in weight. Her illness began three months previously with fever, enlarged glands and sore throat. The patient was admitted then to another hospital where the condition was diagnosed as glandular fever for which she was treated. Several weeks before entering the Morrisania City Hospital the patient developed a rash over the bridge of the nose. Physical examination revealed an acutely ill girl with marked limitation of motion of the back and extremities. At this time there was no erythema on the face. There was a fusiform swelling of the first proximal phalangeal joint and generalized lymphadenopathy. The spleen was palpable. Blood examinations showed leucopenia, anemia and L. E. cells. Chest x rays did not show any significant abnormalities.

A diagnosis of disseminated lupus erythematosus was made

The patient was placed on cortisone 100 mgs daily and after one week s treatment there was some improvement The temperature declined with diminution in the phalangeal swelling and increased motion of the joint However at this time a butterfly erythema appeared on the face (Figure 30A B and C) Cortisone was continued for six weeks but the joint pains soon recurred The patient was then treated with ACTH A week later the patient developed pain in the left chest and soon fluid appeared in the pleural cavity The aspirated specimen showed large numbers of eosinophils and mononuclear cells no other abnormal cells Cortisone treatment was resumed, 100 mg daily but the chest pain persisted and was associated with fever and dyspnea

Two months later the patient developed severe respiratory distress and signs of heart failure The physical and x ray examinations now revealed fluid in both pleural cavities as well as in the pericardium (Figure 30D) The presence of the latter was confirmed by needle aspiration which revealed blood

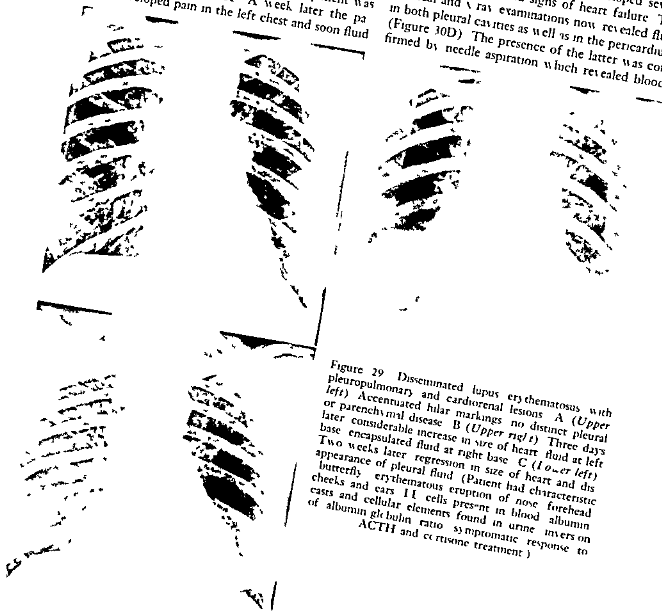


Figure 29 Disseminated lupus erythematosus with pleuropulmonary and cardiorenal lesions A (*Upper left*) Accentuated hilar markings no distinct pleural or parenchymal disease B (*Upper right*) Three days later considerable increase in size of heart fluid at left base encapsulated fluid at right base C (*Lower left*) Two weeks later regression in size of heart and disappearance of pleural fluid (Patient had characteristic butterfly erythematous eruption of nose forehead cheeks and ears LE cells present in blood albumin casts and cellular elements found in urine inversion of albumin globulin ratio symptomatic response to ACTH and cortisone treatment)

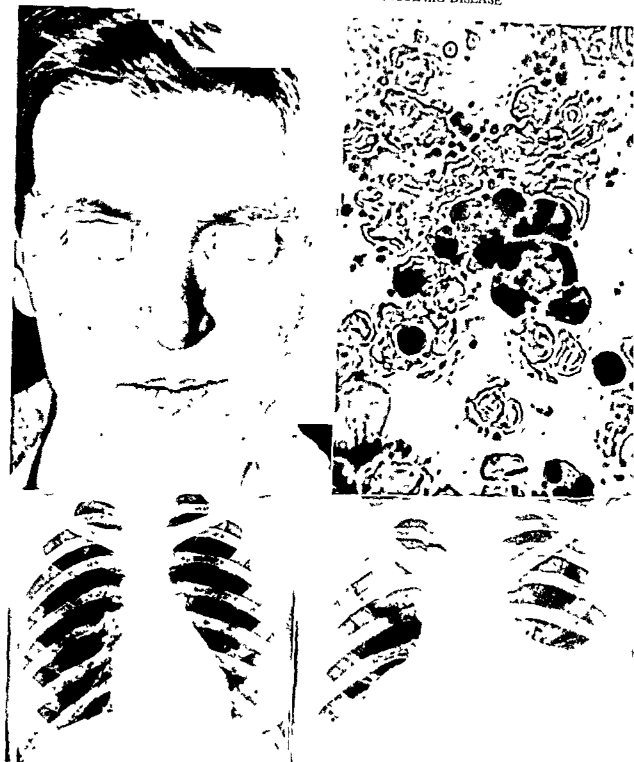


Figure 30 *Case 19* Disseminated lupus erythematosus with pleuropulmonary and pericardial lesions A (*Upper left*) Characteristic butterfly rash on bridge of nose and cheeks B (*Upper right*) 'L E ' cluster and polymorphonuclear cell containing masses of homogenous material C (*Lower left*) Chest x ray shows no abnormalities D (*Lower right*) Five months later, faint, round infiltration in right upper lobe, linear striations in right lower lung field, fluid in both pleural cavities, cardiac shadow enlarged with pericardial effusion (Autopsy revealed *fibrinous, gelatinous exudate in both pleural cavities and in pericardial cavity, edema and congestion of lungs, glomerular lesions of kidney with suggestive* "wire-loop" appearance)

tinged serous fluid In addition the chest x ray now revealed a soft round homogeneous density in the right upper lobe as well as linear streaks paralleling the small fissure For a time the patient showed signs of improvement and she was treated at home with cortisone and periodic chest aspirations Later the patient developed anasarca which was partially relieved with mercuhydrin She was readmitted to the hospital On July 19 1951 the patient sustained a severe nasal hemorrhage and died

Autopsy revealed marked fibrous adhesions within the thorax binding down the viscera The lungs were covered by a thick gelatinous fibrinous exudate which dipped between the lobes of both lungs On cut section the lungs were markedly congested firm and atelectatic There was a frothy sanguinous exudate expressed from the cut surface The fibrinous gelatinous exudate also covered the pericardium which was intimately attached to the heart Exudate was present on the surface of the heart but the valves were normal Microscopic examination revealed the pleural surface thickened by fibrin with minimal exudate no eosinophils were seen The lung parenchyma showed edema and congestion The final diagnosis was disseminated lupus erythematosus with pericardial and pleuropulmonary involvement

Mycosis Fungoides

Mycosis fungoides is a disease characterized by erythematous eczematoid urticarial or mixed lesions of the skin which gradually infiltrate and thicken the epidermis in time producing nodular ulcerative or fungating masses As is often the case in dermatology mycosis fungoides is a misnomer The disease is neither a mycotic infection nor a fungating tumor nor is it limited to the skin Some investigators consider mycosis fungoides a tumor like disease others include the condition among the lymphoblastomas because the terminal picture may assume the features of Hodgkin s disease lymphosarcoma or lymphatic leukemia Bluefarb lists nine diverse opinions regarding the nosologic status of mycosis fungoides and adds a tenth namely that it is a disease of the reticuloendothelial system an opinion shared by many others All agree that the skin lesions are simply an outward expression of a generalized disease Bermin in a review of sixty cases reported in the literature from 1928 to 1938 found that of eighteen cases examined at autopsy sixteen had involvement of internal organs and one probable involvement The organs most often affected are the spleen liver and lungs

Kuznitzky in 1916 was among the first to direct attention to the pulmonary lesions in mycosis fungoides The three cases he described showed roentgenologically prominent hilar markings and infiltrations of the adjacent lung parenchyma In 1940 Werth reviewed the pulmonary findings of mycosis fungoides and found reports of thirty one cases which contained reference to the lungs but very few of these included chest x rays The paucity of adequate descriptions of the pulmonary manifestations is undoubtedly due to the failure of most dermatologists to have chest x rays taken of patients with skin diseases This is forcefully illustrated in a recent study of Bluefarb and Steinberg who reported no less than four cases of mycosis fungiodes in which round infiltrates were demonstrable in the lungs roentgenologically In three the nature of the pulmonary involvement was verified at autopsy, the fourth showed clearing of the infiltrations following nitrogen mustard and radioactive phosphorus The following case illustrates the pulmonary findings in mycosis fungoides

Case 20 Male—Age 59

A white male was admitted to the Montefiore Hospital with a skin disease of three years duration The disease had made its initial appearance on the right leg The lesions soon increased in number became fungating and covered almost the entire body (Figure 31A) Biopsy of skin tissue revealed papillary protrusions extending for some distance into the corium where large numbers of lymphocytes and plasma cells were arranged about the small vessels and about the hair follicles The cells were in edematous loose fibrillar connective tissue The picture was considered in keeping with early infiltrative mycosis fungoides Except for the skin lesions no other significant abnormalities were found A chest x ray at this time revealed a circumscribed infiltration in the right upper lobe and ac



Figure 31 *Case 20* Mycosis fungoides with pulmonary lesions A *(Left)* *Nodular and ulcerative lesions of* skin of trunk arms and legs (Biopsy of skin revealed changes consistent with mycosis fungoides) B *(Right)* Chest x ray reveals a large collection of fluid in the right pleural cavity scattered rounded densities in both lungs (At autopsy lungs revealed numerous small well demarcated nodules also involvement of regional lymph nodes vertebrae liver spleen kindeys and adrenals)

centuation of the bronchovascular markings in both lungs

A year after admission the patient developed *fluid in the right chest which was aspirated and* found to be a clear exudate containing large and small mononuclear cells but no bacteria The chest x ray now revealed in addition to the collection of fluid scattered rounded infiltrations in both lungs (Figure 31B) In spite of radiotherapy the course of the disease was steadily downhill and the patient died twenty one months after admission *Autopsy revealed fluid in both pleural cavities.* The lungs contained numerous small well demarcated firm nodules some with reddish centers the intervening tissue was emphysematous Histologic ex*amination revealed tumor nests of polyhedral cells* in the pleura as well as in the lungs The skin showed similar masses of tumor cells invading and replacing the normal connective tissue bundles of the corium The cells were irregular pyknotic with large hyperchromatic nuclei They assumed a definite perivascular arrangement In addition there was involvement of the regional lymph nodes vertebrae liver spleen kidneys and adrenals

Neurocutaneous Diseases

There are a number of syndromes grouped under this heading which have long been fa*vorite topics of discussion by dermatologists* and neurologists Of late internists have become aware of these intriguing diseases because they may be associated with systemic manifestations including Addison s disease acromegaly myxedema and other disturbances The several conditions include developmental defects neoplastic formations as well as endocrine gland involvements As might be expected mental deficiency and epilepsy are frequent With increasing use of routine chest x rays physicians interested in chest diseases have occasion to encounter pulmonary lesions associated with these neurocutaneous syndromes

The neurocutaneous group of diseases include a variety of disorders involving a mixture of

structures and tissues They are all probably closely allied, some manifesting themselves externally, others internally Heublein and coworkers distinguish four major neurocutaneous entities (A) Tuberous Sclerosis, (B) Von Recklinghausen's Neurofibromatosis, (C) Angiomatosis Cerebri Associated with Trigeminal Nevus, and (D) Von Hippel-Landau's Disease To date, only the first two have been found associated with intrathoracic manifestations

A case reported by Budenz had neurofibromatosis of the skin, tuberous sclerosis and caseous lesions in the calvarium ribs, humeri and femora, multiple polyposis of the colon and a mediastinal tumor Two cases of Von Recklinghausen's disease with bone manifestations were reported by Uhlmann and Grossman in one of which the chest x-ray revealed a large cervical mass involving the upper mediastinum with decalcification, atrophy and deformity of the adjacent cervical vertebrae Other features in the cases included cystic changes in the mandible, gigantism and bowing of the tibia associated with elephantiasis of the lower extremity and oseoporosis A number of other cases have been described featured by bizarre combinations of organ and tissue involvements

Tuberous Sclerosis

This is a rare condition characterized by the following mental deficiency, epileptiform seizures an aceneform rash of butterfly distribution on the face (adenoma sebaceum or Pringle's disease) and tumors which may affect various parts of the body especially the brain, kidneys and eyes Periungual and subungual fibromas as well as skeletal changes are often encountered Pathologically the disease is featured by potato-like sclerotic patches involving chiefly the surfaces and ventricles of the brain,—hence the name, tuberous sclerosis Calcified areas in the calvarium and within the brain substances may be demonstrable roentgenologically

In 1938 Berg published an example of cystic disease of the lungs and several years later, in association with Vejlens and Zachrisson reported three cases of tuberous sclerosis showing peculiar cystic changes in the lungs Particularly interesting was the discovery of the disease in two sisters, both of whom had adenoma sebaceum of the face and ungual fibromas of some of the fingers and toes A brother of these two sisters also had adenoma sebaceum and calcifications of the brain A familial occurrence of the disease has been noted by others The chest x-ray of one of the sisters who later died of asphyxia and in whom it was possible to verify the diagnosis at autopsy, revealed "a well-defined net-like pattern symmetrically spread over both lung fields, caused by closely situated, round translucencies, some so small as to be hardly visible, others varying in size up to that of hazel-nuts The translucencies were separated by relatively narrow, thin septa" The pathologic changes were in keeping with the roentgen findings The lung parenchyma was the seat of innumerable large and small cysts On histologic examination the involved lung was found to consist of connective tissue, blood vessels and, quite strikingly, smooth muscle elements having an unmistakable character of tumor tissue Tumorous changes were also found in the brain and kidneys The films and lung specimens of the patients reported by Berg, Vejlens and Zachrisson, also by Ackermann, also by Silverstein and Mitchell are almost identical The cystic changes in the lungs resemble roentgenologically those seen in histiocytosis and in cystic lungs described in Chapter 3

In a comprehensive review of the pulmonary manifestations of tuberous sclerosis and its relationship to other forms of the disease, Dawson described four cases of pulmonary tuberous sclerosis and analyzed the findings of nine reported by others The chief features were the predominance of the disease among women The pulmonary symptoms were characterized by progressive shortness of breath recurrent pneumothorax, occasional hemoptysis and an absence or late development of concomitant infection The roentgen findings consisted of diffuse miliary or small cystic changes Death followed about five years after the onset of symptoms due to asphyxia from lung destruction or as a result of a spontaneous pneumothorax or right heart failure The pathological changes seen in lung biopsy specimens from two of the cases studied by Dawson



Figure 32 *Case 21* Tuberous sclerosis with pulmonary lesions A (*Left*) Symmetric eruption on the nose adjacent cheek and to a lesser extent chin and forehead B (*Right*) Warty swellings of subungual fibromas with ridging of the nails (*Continued on next page*)

corresponded with previous descriptions of the disease The changes consisted of profuse over growth of connective tissue including smooth muscle and blood vessels leading to the formation of numerous small cysts The following is an abstract of the history and lung biopsy findings of one of the cases of tuberous sclerosis reported by Dawson

Case 21 Female—Age 30

During a period of three years the patient had recurrent seizures of chest pain and dyspnea At the time of the recognition of her disease in the course of a routine chest x ray the patient had the seventh such episode The chest x ray at this time revealed a partial left sided pneumothorax with a small pleural effusion The past history revealed that at the age of five years the patient developed a facial eruption which became more conspicuous in the subsequent five years From the age of eight to ten years the patient suffered from recurrent Jacksonian convulsions but she never lost consciousness

Physical examination revealed a symmetric eruption of the skin of the nose and adjacent cheek and to a lesser extent the chin and forehead In the left lumbar region there was a small patch of peau chagrine The nails of three fingers and eight toes were deformed by warty swellings arising from the lateral edges of the nail base (Figures 32A and B) No abnormalities were found elsewhere except for a moderate enlargement of the kidneys which were deformed by several rounded lumps Examination of the urine was negative Additional [illegible]

The left fibula showed subperiosteal thickening and an oval translucency at its lower end Several of the phalanges showed subperiosteal nodes Excretion urography confirmed the presence of renal



Figure 3[illegible]C Chest x ray (enlarged view of portion of lung) shows several small groups of cysts and generalized reticulation. (*Continued on next page.*)

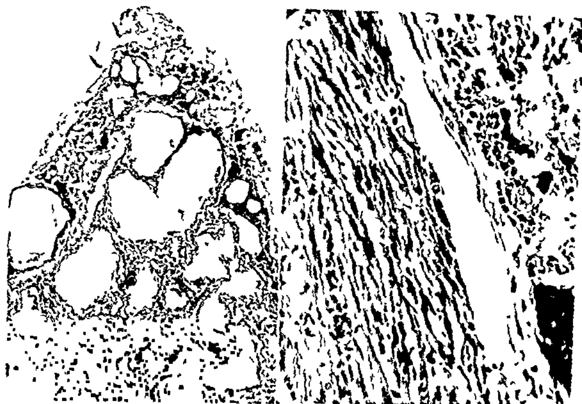


Figure 32D (*Left*) Biopsy specimen from right lung shows cyst like spaces E (*Right*) Biopsy specimen from left lung shows a band of smooth muscle fibers to the right is a strand of fibroblasts and a collection of macrophages loaded with iron pigment (From Dawson *Quart J Med*, 23 113, 1954)

enlargement and showed deformity of the lower calyces on the right side The patient returned home and went to work She soon developed another spontaneous pneumothorax on the left side and after an interval of nine months an eighth seizure of chest pain and dyspnea this time the pain on the right side

On readmission to the hospital the patient showed a right sided pneumothorax with complete collapse of the lung The lung did not reinflate because of the presence of a bronchopleural fistula A thoracotomy was done The lung was found deeply colored dark blue, the surface covered by miliary nodules probably caused by subpleural blebs A biopsy specimen was taken The pleural layers were painted with 5 per cent silver nitrate solution and shortly thereafter the lung reexpanded A month later a spontaneous pneumothorax recurred on the left side The chest was opened and the appearance of the lung was the same as that seen previously on the right side A biopsy specimen was removed Both pleural layers were painted with 5 per cent silver nitrate solution and the lung reexpanded fully within five days

Histological examination of the right lung biopsy showed condensed lung tissue with cyst like spaces, several incompletely lined by cuboidal epithelium (Figure 32D) The left lung biopsy specimen presented a spongy appearance due to small spherical cysts These were lined by low columnar or cuboidal epithelium In addition there were completely solid areas composed of cuboidal cells together with small bands of smooth muscle fibers and fibroblasts (Figure 32E) In the sections of the left and right lungs there were large numbers of iron pigment containing macrophages lying free in the cysts and alveoli as well as within the lung parenchyma probably due to hemorrhages from the vascular walls of the lung cysts A finger biopsy specimen showed squamous cell papilloma

Von Recklinghausen's Disease
(*Neurofibromatosis*)

This disease, described by its discoverer in 1882, is most often seen in the form of multiple fibromas and neuromas in the skin with or without cutaneous pigmentation Neurofibromata

within the thoracic cavity may be encountered as part of a generalized process affecting the skin, sensory, skeletal and other organs Heublein and co workers emphasize the striking similarity between tuberous sclerosis and Von Recklinghausen s neurofibromatosis These authors quote Zimmerman to the effect that tuberous sclerosis is actually a central form of Von Recklinghausen s disease while Von Recklinghausen's disease is a form of peripheral tuberous sclerosis

Intrathoracic neurofibromata have been found in association with intercostal, the vagus and sympathetic nerves The lungs themselves are rarely involved even when the disease is widespread in other organs The reader is referred to a complete review of the subject in a study by Kienbock and Rosler In the thorax, the favorite location of these tumors is in the upper chest, retropleurally, adjacent to the spine The tumors are usually discovered accidentally in routine chest x-rays (Figures 33A and B) During World War II a sizable number were detected in this manner among inductees A tentative diagnosis of neurogenic tumor is made because of the location of the tumors in the posterior portion of the chest adjacent to the spine, a definitive diagnosis can be established only after surgical exploration Approximately 10 per cent of intra thoracic neurogenic tumors undergo malignant changes. The tumors are of special interest to thoracic surgeons and quite a number have been removed successfully The tumor may have an hour glass extension in the spinal cord The lung parenchyma is rarely involved Kent and his co-workers collected seventy-eight cases of primary intrathoracic neurogenic tumors reported in the literature with an incidence of 15 3 per cent of malignancy

An unusual instance of solitary benign neurofibroma within the substance of the lung which was removed surgically was reported by Touroff and Sapin in 1949 A search of the literature by these authors revealed another case, published by Bartlett and Adams in 1946, of a solitary neurogenic tumor attached to the left main bronchus The tumor a neuronoma was removed by pneumonectomy The third case, cited by Touroff and Sapin, was the following instance of multiple neurofibromata limited to the lungs, described by Aronson and myself in 1940

Case 22 Female—Age 57

A Negro housewife was admitted to the Morrisania City Hospital on September 12, 1934 Her chief complaints were asthma like seizures precipitated by upper respiratory infections The present episode lasted about a week and was associated with pain in the left chest dyspnea, cough and bloody expectoration Past history revealed an attack of right sided pleurisy following influenza in 1917 She had an abdominal hysterectomy, salpingo oophorectomy and appendicectomy in 1916 For about ten years, the patient had known that she had diabetes

The patient did not appear acutely ill The temperature and pulse were not elevated The heart was moderately enlarged, blood pressure 180/90 Blood Wassermann was 3 plus Blood examination showed moderate anemia and slight leukocytosis The urine contained 3 plus glucose no acetone and a few pus cells A chest x ray disclosed a number of sharply circumscribed homogeneous densities of varying size, irregularly distributed in both lung fields The appearance of the nodules was in keeping with a metastatic neoplasm Examination of the gastrointestinal, urogenital and skeletal systems failed to reveal a possible primary site After an uneventful stay of six weeks in the hospital the diabetes being controlled by diet, the patient was discharged The final diagnoses were diabetes mellitus, syphilis, essential hypertension, pulmonary metastases from an unknown site

Four years later the patient was readmitted to the Morrisania City Hospital with fever and chills of four days duration There was a moderate elevation of temperature but otherwise no significant changes from those noted on the first admission A chest x ray revealed the round densities in both lungs identical in size and distribution with those noted four years previously Metastatic carcinoma seemed hardly likely and a careful search was made for an underlying cause A mild cystitis and pyelitis were the only abnormalities found Shortly after admission the patient developed increased cough pain in the chest and bloody expectoration A needle was inserted into the right lung at the angle of the scapula and about 10 cc of greenish, moderately thick pus aspirated without difficulty Culture of the pus showed staphylococcus albus

A chest x-ray taken eight days after the thora-



Figure 33 Intrathoracic neurogenic tumor (discovered accidentally on routine fluoroscopy, no symptoms referable to chest) A and B (*Upper left and right*) Large, oval, homogeneous density occupying upper half of right chest calcification of lower border, thickened horizontal fissure, osteoarthritis of thoracic spine C (*Lower left*) One month after excision of tumor, right lung completely reexpanded, interlobar fissure drawn upward pleuritic reaction at right base D (*Lower right*) Resected specimen (At operation a large, spherical tumor was found attached by a pedicle to the paravertebral gutter in the region of the second intercostal nerve Upon removal of the mass, the lung expanded completely and filled the hemithorax The tumor, a soft cyst weighing 1050 grams was filled with slightly blood tinged serous fluid, cyst capsule was thick and contained many foci of calcification Microscopic examination showed histologic features of a neurofibroma)

centesis revealed a collection of air surmounting a fluid level at the site of the lung puncture (Figure 34A). Apparently a broken down mass in the lung had been partly evacuated. The patient's course continued progressively downhill with high fever and repeated hemoptyses. The diabetes became uncontrollable. The patient began to complain of headache and stiffness of the neck. Spinal puncture revealed cloudy fluid containing about 2 000 leukocytes per cc. No organism could be cultured. The patient died December 27 1938 with symptoms of basilar meningitis.

At autopsy, aside from a markedly purulent meningitis at the base of the brain, the lungs were the only organs to reveal abnormalities. The pleural cavities contained no fluid. The left pleural cavity had a few small adhesions at the apex but was otherwise free. The right lung had a moderate number of adhesions over the posterolateral aspects. The lungs were crepitant throughout. Scattered over the surface of both organs were numerous projections of tissue varying in size from 0.5 to 3 cm. These projections, flat with the lung surface, had narrow pedicles by which they were attached to the lungs. On section they appeared to be yellowish and somewhat firmer than fat tissue. Sections of both lungs revealed numerous nodules within the parenchyma of the same type as found on the surface of the lungs (Figure 34B). In the right lung one of the nodules, about 3 cm in diameter, was found to contain a cavity filled with purulent material.

A careful histological study was made of the structure of these nodules by Dr G A Jarvis of the New York State Psychiatric Institute and Hospital. It was Dr Jarvis' opinion that the tumor was a neurofibroma. The typical association of elongated fibres left little doubt as to the diagnosis. The absence of nerve fibres and the arrangement of cells and fibres indicated that the tumor belonged to the type A neurofibroma of Antoni. According to Penfield's classification the tumor could be classified as a "perineural fibroblastoma."

Before concluding the section on the pulmonary manifestations of certain neurocutaneous diseases, it may be in order to refer briefly to the occasional association of bronchiogenic carcinoma and myasthenia gravis. Anderson and co-workers published the case of a man of forty-seven who developed progressive muscle weakness, transient diplopia, difficulty in swallowing and other evidence of myasthenia gravis, the diagnosis being supported by symptomatic improvement after oral treatment with neostigmine. The chest x-ray revealed collapse of the right upper lobe with enlargement of the right hilar and paratracheal lymph nodes. A bronchial biopsy showed carcinoma. On another occasion the same author encountered a comparable instance in which a peripheral neuropathy, similar to myasthenia gravis, disappeared after the removal of a bronchial neoplasm. Following the appearance of Anderson's report, Mackenzie also Shafer cited similar instances of myasthenia gravis associated with bronchiogenic carcinoma. In one case the diagnosis was proved by pneumonectomy, in the other at autopsy.

It may be pertinent to mention the frequent finding of abnormalities of the thymus in patients with myasthenia gravis. Blalock and co-workers estimate that the combination occurs in approximately half of the patients examined at autopsy. On the basis of this apparent relationship Blalock and others have utilized total thymectomy in the treatment of myasthenia gravis. Ross reported the results of thymectomy in 100 patients with myasthenia gravis due to simple hyperplasia of the thymus. Various degrees of improvement, as judged by the reduction in daily neostigmine requirements after operation, were obtained in 87 per cent. The results of thymectomy depend to a large extent on the duration of the disease preceding the operation, the shorter the period the better the chances of improvement.

Although not directly related to the subject under discussion, it might also be mentioned that bronchiogenic carcinoma may be associated with peripheral neuritis. In the opinion of Lennox and Prichard such an association is probably not a matter of coincidence. Since the incidence of bronchiogenic carcinoma is rising precipitously, chiefly in elderly persons, any possible relationship of muscular and neurological abnormalities will have to be studied with particular care to exclude the factor of chance association.

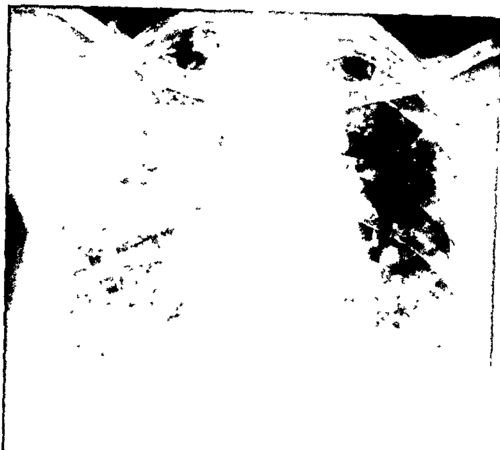


Figure 34A (*See legend on opposite page*)

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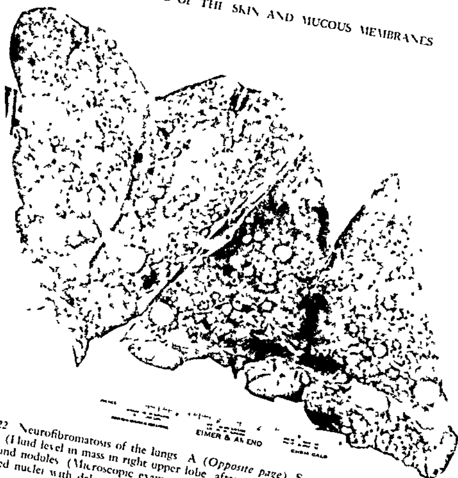


Figure 34 *Case 22* Neurofibromatosis of the lungs A (*Opposite page*) Scattered, round densities of uneven size in both lungs (Fluid level in mass in right upper lobe after needle aspiration) B (*Above*) Lung Section shows multiple round nodules (Microscopic examination of nodules showed fibres and cells in palisade arrangement also elongated nuclei with delicate fibres and small cysts lined by endothelium) (From Rubin and Aronson *Am Rev Tuberc* 41 801 1940)

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Chapter 8

Diseases of the Skin and Mucous Membranes (Continued)

Diseases of the Skin and Malignant Tumors

In an instructive exhibit Curth collected a variety of non neoplastic dermatoses which may be associated with malignant internal tumors Of particular interest from the viewpoint of the present discussion are the skin diseases which may be found in association with intrathoracic tumors

In reviewing the various dermatoses which may be associated with neoplastic disease one is struck by the fact that collagen diseases appear to be favored Since collagen is the major component of the integument such an association is to be expected However the relationship is at times so striking that other factors are undoubtedly also involved Lansbury commented on the association of neoplasms including bronchiogenic carcinoma and rheumatoid arthritis dermatomyositis and disseminated lupus erythematosus As will be indicated shortly scleroderma also falls in this group

Lansbury speculates that inasmuch as invasion is a feature common to all neoplasms and since in some cases the collagen diseases disappear after the tumor is removed the association of the two may be caused by some factor which facilitates the invasion of malignant cells This factor Lansbury suggests might be related to some hyaluronidase like substance secreted by malignant cells The substance after entering the general circulation may interfere with the hyaluronate components of connective tissue and their enzymes and coenzymes It would seem therefore good practice when a collagen disease occurs in an older person without a recognizable cause that studies should be made to detect a possible concealed neoplasm

A Negro female aged sixty one years presently at the Bronx Municipal Hospital Center developed two years prior to admission a tingling sensation and pain in the hands and feet At this time a chest x ray disclosed active pulmonary tuberculosis and the patient was placed under treatment with streptomycin and isoniazid with considerable improvement in the pulmonary disease A year later the pain in the extremities became worse The skin of the fingers and toes showed atrophic changes with some deformity of the phalanges a picture of acrosclerosis Two skin biopsies revealed subepithelial fibrillar fibrosis hyaline and some amyloid material also focal edema and vasculitis The dermal changes were in keeping with scleroderma The bones of the hands and feet showed roentgenologically deossification and soft tissue changes also calcification of blood vessels At one of the staff conferences the problem was raised of the possible relationship of certain diseases of the skin and occult carcinoma Three months later in the course of a careful examination a member of the house staff found a peculiar friable nontender granulomatous tissue mass in the floor of the patient s mouth A biopsy revealed a papillary squamous cell carcinoma Although the changes in the skin and the appearance of the carcinoma in the mouth of this patient may have been coincidental this experience is included among those reported by others to indicate that possibly there is an association of certain dermatoses and malignant neoplasms

The records of the Montefiore Hospital in the past fifteen years contain four instances of scleroderma in association with malignant neo-

plasms. In one case a man of fifty-two with scleroderma had a complicating squamous cell carcinoma of the hands. Another man of forty-one had a fibrosarcoma of the left upper extremity engrafted on a sclerodermatous process. The arm required amputation. The patient died and at autopsy the neoplasm was found generalized in the body. In a woman of forty-three with scleroderma a pulmonary carcinoma was found. In another woman of fifty-six with an eighteen-year history of scleroderma and Raynaud's disease a pleural effusion developed. A thoracoscopy revealed metastatic adenocarcinoma of the pleura probably originating in the gastrointestinal tract. Zatuchni and co-workers reported three cases of scleroderma with diffuse interstitial fibrosis and primary cancer of the lungs. In each instance the neoplasm was a terminal bronchiolar carcinoma. The predisposition of patients with dermatomyositis to develop malignant neoplasm, the two often progressing synchronously, will be discussed later.

In addition to collagen diseases Curth draws attention to a number of other dermatoses which may be associated with intrathoracic and other neoplasms. Pachydermoperiostosis has been found in association with bronchogenic carcinoma. This skin disorder is found predominantly in males and is characterized by skin changes which resemble those of acromegaly and roentgenologic findings in keeping with hypertrophic pulmonary osteoarthropathy. Curth also notes that with the development of erythema gyratum repens, a disorder characterized by wavy, knotty, pine-like gyrations in the skin, a primary or metastatic tumor may be found in the breast or lung. Patients with generalized itching may later show signs of internal neoplasms and malignant lymphomas. The itching which may be accompanied by urticarial wheals is probably due to allergens or toxins released by the tumor. Acquired ichthyosis is encountered in patients with Hodgkin's disease or lymphosarcomas, the cutaneous eruption being ascribed to liver damage and impairment of vitamin A metabolism.

Curth points out that, while disappearance of the dermatosis after removal of the tumor and reappearance of the dermatosis with recurrence of the tumor point to some causal connection between tumor and dermatosis, it would be wrong to assume the tumor to be the sole cause of the cutaneous eruption in every such instance. The catabolic substances of the neoplasm may serve as the trigger mechanism for skin predisposed to various pathologic processes by genetic, allergic or other factors.

Scleroderma

For years dermatologists have been intrigued by occasional encounters with patients, usually young women, possessing a peculiar leathery hard skin (scleroderma). Of late increasing attention is being paid to the condition by physicians at large because of the realization that the skin lesions in this disease are only an outward expression of a profound systemic disturbance which may affect various organs and tissues.

The change in skin texture is usually noted first on the hands, later the face, neck and upper trunk. Two major types of scleroderma are recognized: a circumscribed and a diffuse progressive form. The latter is in most instances a cutaneous manifestation of a systemic disease which according to Goetz should properly be called progressive systemic sclerosis. As mentioned, the disease may affect a wide variety of tissues and organs including the gastrointestinal tract, particularly the esophagus; the osseous system, particularly the terminal phalanges of the fingers; the skeletal muscles, thyroid, kidneys, heart, lungs and other structures (Figure 35). In addition the disease is often featured by the deposition of calcium salts in soft tissues, a condition known as calcinosis. The resulting induration and stiffening of the affected parts interferes with proper functioning of the organs, leading to various symptoms and complications.

A number of theories have been proposed to explain scleroderma. In an exhaustive study based on an analysis of over 150 cases of scleroderma, Leinwand and co-workers group the possible etiological factors into four main cate-

gories (1) endocrine dysfunctions, (2) nervous system disturbances, (3) toxins, infections and trauma, and (4) vascular disease As yet, no single explanation suffices Scleroderma is commonly included among the collagen diseases and represents the least virulent member of the group

Pathology

The morphological changes in scleroderma follow a fairly uniform pattern The hardening of the skin and mucous membrane is the end result of a process which begins as a diffuse, nonpitting edema of the connective tissue After the edema fluid absorbs, the stroma is replaced by fibrous tissue leading eventually to atrophy of the skin and underlying structures An accompanying vascular disturbance manifests itself in arteriolar spasm and obliteration of small blood vessels with a corresponding reduction of blood flow to the parts If the process affects the skin supplied by the digital arteries a fairly frequent accompaniment, the scleroderma may be associated with Raynaud's disease The latter may precede recognizable sclerodermatous changes in the skin A fully developed picture of scleroderma is featured by a mask-like face, the lips puckered so that smiling is difficult the skin smooth and glistening with mottled pigmentation at times depigmentation, about the nose and mouth The hands may show the stigmata of Raynaud s phenomenon with absence of digital phalanges

The pulmonary lesions in scleroderma as in the other organs affected, is characterized by a sclerotic process which manifests itself either (1) as a diffuse interstitial fibrosis with thickening of alveolar walls, also obliteration of air spaces and compensatory emphysema, or (2) a similar picture accompanied with cystic sclerosis of the parenchyma, probably representing a further stage in the development of the disease The cystic spaces are caused by hyaline degeneration of alveolar walls which become thinned out and rupture causing dissolution cysts Bullous emphysema and bronchiectasis are occasionally seen The pulmonary blood vessels, including the alveolar capillaries may be encased in a collagenous sheath with obliteration of capillaries and alveolar spaces There is reason to suspect that some cases of, so called, indeterminate forms of diffuse interstitial fibrosis and cystic disease of the lungs, of unknown origin, may be caused by sclerodermatous changes of these organs although skin changes may be absent There are analogues for this state of affairs in sarcoidosis and several other diseases mentioned in this volume

Clinical Features

Hayman and Hunt found reports of seven cases of scleroderma in which symptoms referable to pulmonary involvement were present before the development of the skin disease or at a time when the cutaneous changes were so slight as to escape notice Raynaud s phenomena preceded pulmonary symptoms in four of these cases, in the remaining three the pulmonary symptoms occurred as the initial manifestations of the disease In two cases the time interval between the respiratory and cutaneous manifestations was more than two years Prowse reports the case of a man of sixty-six who, one year before the appearance of clinical signs of scleroderma developed "pneumonia and pleurisy" on one side and, two weeks after recovery from this episode 'pneumonia and pleurisy" on the other The chest x rays were interpreted as in keeping with chronic bronchitis and emphysema The postmortem examination showed in addition to scleroderma of the skin, fingers, hands and lips a marked degree of interstitial fibrosis of the lungs and thickening of alveolar walls which were considered in keeping with scleroderma

The symptoms of scleroderma of the lungs reflect the anatomic changes in the thoracic cage as well as the effects of stiffening of the lungs with resulting interference in the bellows action of the organs Dry cough, dyspnea and cyanosis become increasingly severe as more alveolar epithelium is compromised in the fibrotic process Orthopnea appears with a failing heart Death may follow acute asphyxia or as a result of chronic cor pulmonale The heart itself may of course, be the seat of sclerodermatous changes and contribute to the demise At any stage, an intercurrent respiratory infection may terminate the course of the disease

Roentgenology

The roentgenological appearance of scleroderma of the lungs are not specific but they assume added significance in the light of the clinical findings. In the presence of emphysema the chest x-ray may fail to reveal much deviation from the norm although widespread interstitial changes may be present in the organs. In uncomplicated cases both lungs show either fine or coarse striations affecting diffusely both organs. The changes are most pronounced in the inner [illegible]

cystic changes the affected lungs may or may not show a fine honeycombing. In the late stages of the disease the pulmonary changes become even less distinctive roentgenologically. This is due to recurring pulmonary infections and suppuration. The latter is often due to aspiration of contents from the esophagus, this organ being often involved in the process. Sooner or later the lungs reveal evidence of chronic passive congestion caused by a failing heart.

In an instance of scleroderma complicated by Raynaud's disease which I had occasion to follow on the wards of the Morrisania City Hospital and in the Chest Clinic the pulmonary markings appeared so striking and in keeping with the skin disease that after study the case was reported by Murphy, Krainin and Gerson as one of scleroderma with pulmonary fibrosis. This was the first case reported with a description of the pulmonary manifestations of the disease as seen roentgenologically. Unfortunately autopsy confirmation was not available. Subsequent studies by others including postmortem observations have confirmed the conclusions reached in this particular case. In recent years the possible presence of sclerodermatous changes in the lungs in patients with scleroderma of the skin has presented itself to me on a number of occasions. In fact in several I suspected scleroderma of the lungs although skin lesions were not demonstrable. But one cannot go as far as Pugh in claiming that in many cases the roentgenologic diagnosis of pulmonary scleroderma can be made without knowledge of the clinical picture. Even in the presence of scleroderma of the skin it is most difficult to correlate the markings in the lungs with the dermal changes because of the complicating factors previously mentioned.

In the following case the initial symptoms were in keeping with an acute nonbacterial bronchopneumonia. Serial chest x-rays revealed increasing diffuse interstitial fibrosis of the lungs. At the same time the patient developed signs of scleroderma with Raynaud's phenomenon, also evidence of lupus erythematosus, the diagnosis of the latter being confirmed by the presence of L.E. cells in the blood on repeated occasions. The case demonstrates not only the pulmonary findings in scleroderma but also the association of the latter with lupus erythematosus, a kinship stressed in Chapter 6.

Case 23. Female—Age 59

The patient was admitted to the Montefiore Hospital on Dr. Sol Biloon's service in December 1952 with fever, dyspnea and physical signs pointing to an acute pneumonia of one day's duration. A bedside chest x-ray taken on the day of admission revealed massive infiltrations involving both lungs with little air containing tissue to be seen. There was moderate enlargement of the heart (Figure 36B). The impression was that of congestive heart disease and bronchopneumonia since the patient had had a seizure of coronary occlusion four years previously for which she had been treated with low salt diet and diuretics.

The patient received large doses of penicillin and streptomycin but the temperature remained elevated for some time and declined slowly. A week after admission the patient experienced a sudden chill, the temperature rose and at this time the patient had pain and tenderness in the abdomen as well as evidence of coldness of the extremities and peripheral cyanosis. The patient experienced several additional seizures of this nature. Of significance in the laboratory findings was the presence of a high degree of macrocytic anemia and a relative leukopenia. The patient improved slowly and was discharged a month after her admission.

At home the patient soon developed pain, swelling and stiffness of the hands and, at times, pain and cramps in the legs. The patient was readmitted to the hospital six months after her discharge be-





Figure 35 Scleroderma associated with diffuse interstitial pulmonary fibrosis and other lesions A Interstitial striations throughout both lungs B Two years later marked increase in diffuse fibrosis scattered irregular densities heart enlarged C Esophagogram showing dilatation of organ (absence of peristalsis and delay in emptying) D (*Opposite page*) X ray of hands showing osteoporosis and atrophy of terminal phalanges (Autopsy revealed diffuse interstitial fibrosis of both lungs patchy bronchopneumonia fibrosis of esophagus and small intestine fibrinoid changes in myocardium)

cause of the sudden reappearance of chills, fever and sweating The physical examination revealed a chronically ill looking woman who appeared older than her stated age There was atrophy and swelling of the fingers and spindling of the terminal phalanges The mouth was pinched and the skin over the forehead tight There was a scaling erythematous rash over the V of the neck with patchy involvement of the trunk and extremities (*Figure 36A*) The erythema became more marked after exposure to light The patient offered the additional information that she had noted cold hands even in warm weather and at times the fingers turned bluish in color

Examination at this time revealed deformity of the finger joints, dullness and rales at the bases of the lungs and moderate liver enlargement. On several occasions pleural and pericardial friction rubs were heard. The chest x-rays revealed increasing diffuse fibrosis of both lungs (Figures 36C and D). Significant laboratory findings included the presence of anemia, leukopenia and positive L. E. tests of the blood on repeated occasions. The patient continued to have low grade fever and showed sensitivity reactions to blood transfusions and drug medication. The final diagnosis was scleroderma associated with Raynaud's phenomenon, lupus erythematosus, rheumatoid arthritis and arteriosclerotic heart disease. Although not fully recovered, the patient left the hospital. Two months later she died suddenly of what was presumed to be an acute coronary artery seizure.

Dermatomyositis

This disease has certain features in common with lupus erythematosus and scleroderma but in other significant respects shows individual characteristics. Dermatomyositis affects more often males of advanced age. The disease involves the skin, subcutaneous tissues and muscles. It may run an acute, but more often a chronic course. The onset is insidious with fatigue, muscle pain, weakness and lassitude. In time, cutaneous changes appear with puffiness of the face and an erythematous rash involving the neck, ears, chest and shoulders. The erythema affects chiefly the dorsum of the hands at the phalangeal joints, the fingers in time becoming stiff and painful. The muscle weakness is bilateral and symmetrical; in advanced stages the muscle weakness may interfere with deglutition and respiration, leading to aspiration pneumonia. Histologically, the affected parts reveal changes of a nonspecific nature consisting of edema of interstitial tissues, lymphocytic infiltration and necrosis of muscle fibers. The changes lead eventually to atrophy and contractures.

The pulmonary changes in dermatomyositis are not a feature of the disease. A careful search of the literature does not reveal any reported in



Figure 35D (*See legend on opposite page*)

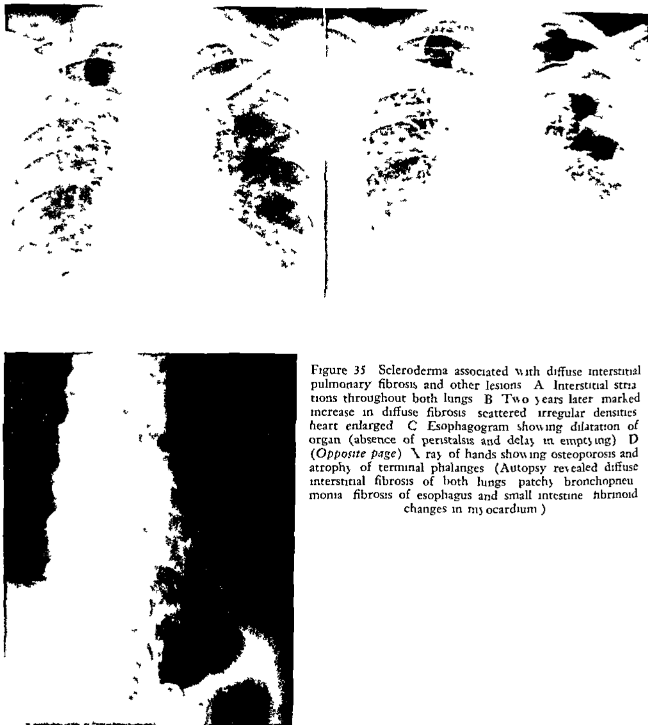


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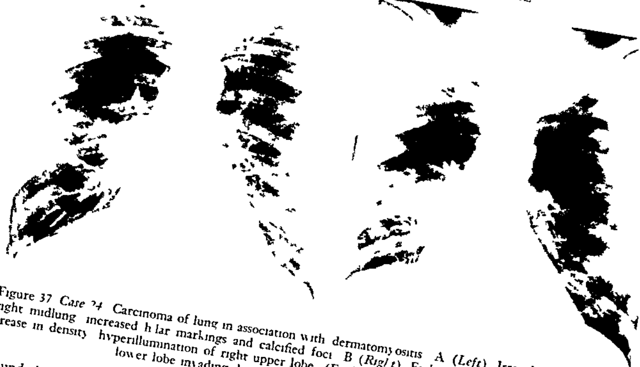


Figure 37 *Case 24* Carcinoma of lung in association with dermatomyositis A (*Left*) Irregular infiltrations in right midlung increased hilar markings and calcified foci B (*Right*) Eighteen months later considerable increase in density hyperillumination of right upper lobe (Exploratory thoracotomy revealed carcinoma of right lower lobe invading diaphragmatic pleura giant bulla in upper lobe)

found shrunken with induration and distention of the subpleural lymphatics The middle lobe was not involved There was a large emphysematous bulla occupying the right upper lobe The parietal pleura was found studded with metastases especially over the diaphragm The hilum was indurated with neoplasm Because of the extensive involvement a resection was impossible Histologic examination of a piece of parietal pleura revealed coalescing metastatic nodules

Following operation the patient continued to complain of muscular weakness pain in the arms also dyspnea nausea and vomiting The erythematous rash noted previously now covered the upper chest arms face as well as hands The patient was admitted to the Montefiore Hospital where a muscle and skin biopsy was obtained from the deltoid region Histologic examination of the specimen revealed atrophy of epidermis with fragmentation focal disruption and dissolution of the immediately adjacent corium There was some thickening of the collagen of the deeper layers of the corium There was edema of the vessel walls and perivascular collections of inflammatory cells consisting of lymphocytes and neutrophiles The vessels affected were generally of arteriolar and precapillary size Individual muscle fibers had lost their coarse striations There was interstitial inflammatory reaction in the muscles the cellular population of which was largely perivascular The tissue changes appeared consistent with the clinical diagnosis of dermatomyositis The patient went rapidly downhill and died

Acanthosis Nigricans

This disease is characterized by the presence of darkly pigmented furrowed areas arranged symmetrically on the exposed surface of the body especially in the axillary inframammary antecubital and crural folds The hyperkeratotic skin and proliferation of epithelium often results in small warty growths Two forms of acanthosis nigricans are recognized (1) a juvenile or benign form occurring in young people especially at the time of puberty and (2) an adult or malignant form occurring in later years The latter is associated with cancer of viscera in ap

proximately 50 per cent Because of the high incidence of malignant neoplasms especially of abdominal viscera some authorities hold that a diagnosis of acanthosis nigricans in an individual of advanced age warrants an exploratory laparotomy

In a review of 395 cases of acanthosis nigricans reported in the literature up to 1943 Curth found the association of cancer reported in approximately one half 93 per cent of the latter being abdominal with carcinoma of the stomach accounting for almost 70 per cent Carcinoma of the lung was reported in only three cases including one described by Levin and Behrman of a man treated at the Montefiore Hospital The remaining two included one discovered accidentally by Dore and one reported by Petrini de Galatz In 1950 Spear reported an additional case of acanthosis nigricans in a fifty year old white man in association with anaplastic carcinoma of the lung

Because of the rarity of carcinoma of the lung in association with acanthosis nigricans the following case which came to my observation is worth citing

Case 25 Male—Age 42

The patient lithographer developed a rash under the chin Later he noted that the skin in the armpits and in the groin became dark and stiff (Figure 38A) The patient was seen by several dermatologists who diagnosed the condition as acanthosis nigricans Of interest in the patient's past history was the fact that since the age of twenty three he had developed gradual loss of eyesight and a sister was also afflicted with loss of eyesight the cause of which could not be determined When I examined the patient the symptoms were moderate cough and bloody expectoration The skin in the folds of both axillae and groins was dry darkly pigmented and ridged with minute papillae projecting above the surface A chest x ray revealed a large homogeneous spherical density occupying the entire superior aperture of the thorax (Figure 38B) Biopsy of a supraclavicular lymph node showed squamous cell carcinoma Radiotherapy was applied but the patient went downhill and died three months later



Figure 38 ... rkly pigmented ... right upper lobe

Scleredema

This disease was first described by Buschke in 1900. In 1932 Epstein gave the first comprehensive review of the subject. Scleredema may follow or be precipitated by acute infections such as scarlet fever, influenza or pharyngitis or the disease may be ushered in with fever and rheumatic symptoms. Several days or weeks after the subsidence of the acute infection the patient develops a rapidly progressive nonpitting edema of the face chiefly about the eyelids which become puffed up. Leinwand described the waxy appearance of the face as if the skin were in a paraffin bath. The edema spreads to the neck, shoulders, arms and abdomen. The disease undergoes spontaneous remission within a variable period of months. In contrast to scleroderma in the edematous stage, with which it may be confused, scleredema spares the hands and feet and almost invariably resolves without causing permanent damage. However, acute dermatomyositis, myxedema, as well as scleroderma may present problems in differential diagnosis. The systemic nature of scleredema has been stressed by Vallee, O'Leary and co-workers, Leinwand and others.

The nature of the pleuropulmonary changes which may be present in scleredema have not been studied in detail because the disease is seldom fatal. However, pleural effusions are often encountered in association with pericardial, peritoneal and joint effusions. A rare instance of generalized scleredema with autopsy findings reported by Leinwand revealed, in addition to fluid in both pleural cavities, diffuse edematous changes of the lungs. Many of the viscera had a peculiar rubbery consistency. Microscopic examination revealed swelling of the collagen with separation of the bundles resulting in clear spaces. There was a notable absence of inflammatory reaction. In four patients with scleredema Vallee noted pleural fluid in two; one had massive effusions in both cavities and the other had, in addition, a pericardial effusion. The fluid disappeared with remission of the cutaneous disease. Vallee believes that intrathoracic effusions are an intrinsic feature of the disease.

Sjogren's Disease

In 1933 and in later publications Sjogren described a syndrome characterized by pronounced dryness of the mucous membranes due to inadequate secretion of glands, especially of the salivary and lacrimal glands. Later studies revealed that the condition may also involve the glands of the respiratory tract, stomach, sweat glands and vaginal mucosa. The major pathological features consist at first of a lymphocytic cellular infiltration producing glandular enlargement and later parenchymal atrophy resulting in impaired function. Eventually both parenchyma and cellular infiltrate disappear and are replaced by a fibroadipose tissue. The participation of the lacrimal and salivary glands may present a picture simulating Mikulicz disease. In fact some authors prefer the term *Mikulicz-Sjogren Disease*. It is suspected that both conditions are related to uveoparotitis and that all three are manifestations of sarcoidosis to be described in the following chapter. The reduced salivation and lacrimation and the resulting dryness of the nose, pharynx, stomach, trachea and bronchi and other mucous membranes may produce distressing symptoms.

Sjogren's disease is believed to be a congenital defect since members of the same family have been found affected. The precipitating factor may be an endocrine disturbance, the condition being particularly frequent in women at the time of the menopause. Sjogren, in one of his early communications, stated that the mucous membrane lesions are part of a generalized disease. The frequent association of rheumatoid arthritis is in keeping with such a concept. Variable degrees of success have been reported with the use of estrogenic and androgenic preparations, corticotropin hormones, cortisone, cholinergic drugs, pilocarpine and other medicaments. The disease is refractory to treatment.

Noteworthy from the viewpoint of the present discussion is the fact that dryness of the bronchial mucosa and associated obstructive phenomena

may cause pulmonary changes of a granulomatous character associated with low grade inflammation Ellman and Weber described the case of a woman, with Sjogren's disease, who developed bilateral dry pleurisy Later, she was found to have abnormal physical findings at both lung bases This was associated with a roentgen picture simulating sarcoidosis Through the courtesy of Dr Henry K Taylor, I had an opportunity to see the chest x rays of a patient with clinical features of Sjogren's disease The film revealed diffuse fibrosis and emphysema of both lungs, especially the right upper In this case, as in the one reported by Ellman and Weber, the patient had also been diagnosed at first as sarcoidosis

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Chapter 9

Diseases of the Skin and Mucous Membranes (Concluded)

Sarcoidosis

Introduction

Sarcoidosis is probably the best example of the thesis under consideration, namely, the lungs may not only mirror an internal disturbance, but they may be the sole organs found involved in what is generally acknowledged as a systemic disease Sarcoidosis was originally described by Hutchinson and later by Boeck in 1899 as a dermatologic disorder The latter designated the condition sarcoidosis, because the histologic changes resembled sarcomatous lesions In time, Boeck s sarcoid was accepted in dermatology as a distinct entity In 1914, Schaumann expressed the view that Boeck s sarcoid or benign miliary lipoid as Boeck subsequently redesignated the disease, was a systemic affliction, a benign lymphogranuloma, which may involve many organs of the body, especially the group comprising the reticuloendothelial system But, in spite of the fact that sarcoidosis is neither a sarcoma nor a lupus-like disorder, nor primarily a skin disease, the designation sarcoid, has been retained chiefly for want of a better nomenclature

Unaware of the singleness of the disease, earlier investigators in various branches of medicine, including neurologists, ophthalmologists, endocrinologists and pediatricians described, from time to time, various facets of sarcoidosis as distinct syndromes of which there are about two dozen listed in the literature The more frequent eponyms under which sarcoidosis has been described include Besnier-Boeck Schaumann s disease (systemic sarcoidosis), Heerfordt's disease (uveoparotid fever), Jungling s disease (ostitis tuberculosa multiplex cystica) and Mikulicz' disease (lacrymal and salivary gland involvement) In recent years the literature on the subject has reached voluminous proportions largely due to the interest focused on the disease following the introduction of routine chest roentgenography in the examination of apparently healthy persons Intrathoracic sarcoidosis is currently a favorite topic of discussion among physicians interested in diseases of the chest It is now established that Boeck's sarcoid, originally described as a skin disease, may affect various organs and tissues of the body without necessarily implicating the skin, in fact, in systemic sarcoidosis the skin is more likely to be spared

Incidence and Distribution

Among uncommon diseases sarcoidosis is frequent, especially the intrathoracic form In 1948 Freiman found more than 1,000 cases of sarcoidosis and related syndromes reported in the literature The disease has long outgrown the stage of individual case reports unless the latter deal with unusual features or are concerned with basic etiologic, immunologic or therapeutic problems The earlier descriptions of the disease stemmed largely from Scandinavian and European countries, in recent years a sizable literature on the subject has accrued in America A comprehensive monograph on sarcoidosis by Longcope and Freiman, published in 1952, is based on a combined investigation of 160 cases, including thirty examined at autopsy, from two institutions alone

Sarcoidosis affects chiefly adults of the third and fourth decades of life but infants and aged are not spared Instances of sarcoidosis have been reported in members of the same family,

including identical twins and running a similar course The disease is found with about equal frequency in the two sexes possibly more often in females In the Scandinavian countries England and on the Continent Nordics are mainly affected In the United States Negroes are particularly vulnerable especially those born in the southeastern states An analysis of approximately three hundred cases of sarcoidosis encountered in the armed forces of the United States revealed sixteen times as many cases of the disease in Negroes as in Whites Other features of the epidemiology of the disease will be discussed in conjunction with the significance of negative tuberculin reactions usually encountered in sarcoidosis

Pathology

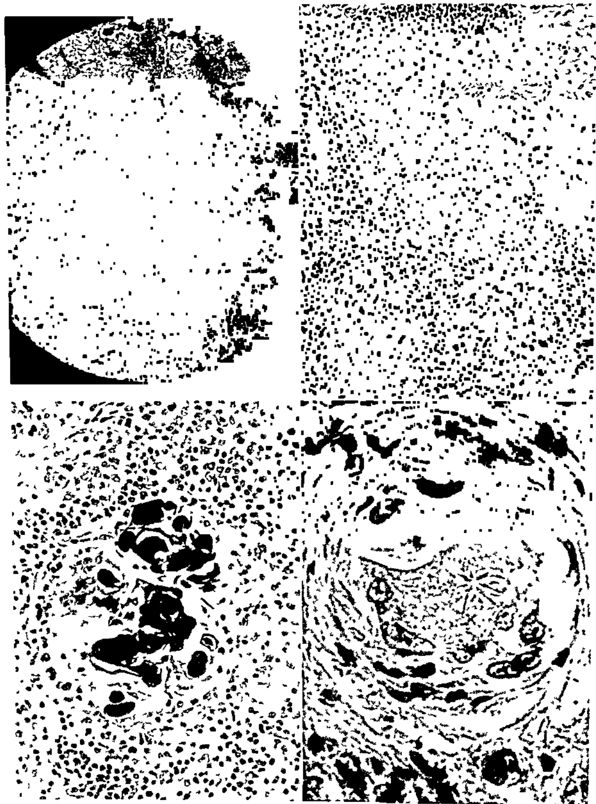
In 1944 Pinner and I reported a case of systemic sarcoidosis the course of which could be followed from childhood to the death of the patient at the age of twenty five The postmortem findings of this patient and of twenty five additional autopsied cases reported by others were described in detail The literature at the time of this writing 1954 contains reports of approximately 150 autopsied cases Ricker and Clark described twenty two cases of sarcoidosis with autopsy findings culled from the files of the Army Institute of Pathology Inasmuch as some of the patients described in the series had died of gunshot and other traumatic injuries and in two thirds the disease had been unsuspected until the postmortem examination the study by these investigators is unusually instructive with respect to the early developmental phases of the disease

The histologic features of sarcoidosis irrespective of the organs or tissues involved are of a monotonous consistency In its classical form the disease is characterized by tubercle like structures composed of epithelioid cells small numbers of lymphocytes and giant cells of the Langhans type (Figure 39A and B) Macroscopically aggregates of these tubercles reveal themselves as disseminated nodules in the affected tissue or organs These cold miliary tubercles were considered at one time to be an expression of noncaseating tubercles Pinner an early advocate of this theory changed his views in his later years preferring the noncommittal term sarcoidosis

According to Ricker and Clark the earliest lesion of sarcoidosis is recognizable especially in the lymph nodes in areas of widening of the lymphoid sinuses and hyperplasia of reticulum cells The affected tissue soon becomes the seat of discrete epithelioid tubercles which are arranged in clusters of approximately the same stage of development There is an absence or a minimal degree of necrosis and no acid fast organisms can be cultured from the tissues The last mentioned feature is decisive in the differentiation of sarcoidosis from tuberculosis unless the latter is superimposed on the former In its protracted course sarcoidosis may affect various organs and tissues of the body at different times so that signs of progression and recession may be present concurrently

In the process of healing the tubercles merge and lose their identity eventually undergoing fibrosis and in many instances diffuse hyalinization the nodules becoming acellular scars In the lungs as in other organs which may be involved one cannot differentiate the diffuse interstitial fibrosis of sarcoidosis from other forms of fibrosis unless one is familiar with the clinical findings and the results of histological and immunological studies It should be emphasized that even when the histologic picture corresponds entirely with that of sarcoidosis a diagnosis cannot be made with certainty inasmuch as epithelioid cell granulomas may be caused by beryllium components silicosis and other agents This aspect will be discussed more fully later The uncomplicated sarcoid lung in which the disease had been evolving for some time shows grossly diffuse fibrosis the parenchyma studded with grayish nodules There is a variable degree of bronchiectasis emphysema and bleb formation On rare occasion →

Figure 39 Sarcoidosis histologic features A (*Upper left*) Noncaseating epithelioid tubercles with scattered giant cells B (*Upper right*) Detail of tubercles C (*Lower left*) (Doubly refractile) Schaumann corpuscle in ruptured giant cell D (*Lower right*) Asteroid body in giant cell



(See legend on opposite page.)

the latter may lead to spontaneous pneumothorax. There are occasionally smooth-walled cavities which show no caseation or sarcoid changes in the walls, the exact origin of which is difficult to ascertain.

In addition to the tubercle-like structures mentioned, the histopathology of sarcoidosis is occasionally featured by the presence of giant cell inclusions. These intracellular inclusion bodies were first described by Schaumann in 1941. The "Schaumann corpuscles" are refractile, stratified and, in some cases, calcific bodies (Figure 39C). They are more apt to be found in lymph nodes but may also be present in other organs, including the lungs. In 1944, Friedman described an asteroid form of inclusion body in the spleen of a patient with sarcoidosis (Figure 39D). Others have encountered such asteroid or radial bodies in other organs also. Schaumann corpuscles have been found in beryllium lesions and asteroid bodies have been found in leprosy, torulosis, histoplasmosis and in foreign body granulomas.

Cunningham found stellate inclusions in giant cells in three types of tissue response: in association with foreign body reaction, tuberculoid granulomatous inflammation and in acute and chronic inflammation and repair. The inclusion bodies found in sarcoidosis are therefore not specific for any disease. Various opinions have been expressed as to the components of these inclusion bodies. Teilum found paramyloid deposits in the reticuloendothelial cells of sarcoidosis similar to those seen in patients with disseminated lupus erythematosus and in those with atypical and experimental amyloidosis. This investigator considers Schaumann corpuscles the result of hyperglobulinotic precipitates in the cytoplasm of the reticuloendothelial cells.

ETIOLOGY

It is beyond the scope of these pages to discuss at length the possible cause or causes of sarcoidosis. Only those aspects bearing on the problem of diagnosis will be mentioned. In an exhaustive review Rosetenberg comes to the conclusion that sarcoidosis, if it is an infectious disease, is most likely caused by a new agent, a disease *sui generis*. It is difficult to conceive of sarcoidosis being a variant of any known existing disease, certainly not tuberculosis, a belief still prevailing *in some* quarters. Rostenberg points out the importance of distinguishing between systematized sarcoidosis and the, multiple caused, pattern reaction known as sarcoid inasmuch as the latter constitutes a commonplace type of tissue response to injury shared by other diseases. Sarcoid-like granulomas may be found in brucellosis, chronic disseminated histoplasmosis, syphilis, tularemia, balstomycosis, leprosy, and other fungous infections, beryllosis and several other conditions.

As mentioned, the sarcoid tubercle resembles superficially the tubercle of tuberculosis but differs from the latter in the paucity or lack of necrosis but more significantly in the fact that pathogenic acid fast bacilli cannot be demonstrated in the affected tissues. Early in the course of sarcoidosis, a coexisting active tuberculosis is rare; late in the disease tuberculosis is found in about 15 per cent of autopsied cases. Interestingly enough, in a case of systemic sarcoidosis with terminal tuberculosis, studied by Pinner and myself, numerous lung sections revealed histologically both noncaseated and caseated tubercles containing giant cells but only in the noncaseated tubercles were occasional calcific bodies found, some of which were ring shaped. Acid fast bacilli were readily demonstrable in the caseated lesions in the lungs, liver, kidneys, vertebra and adrenals. In more than fifty noncaseated, epithelioid tubercles in the lung, liver and spleen no acid fast bacilli could be found. A search for acid fast bacilli in lymph node lesions was entirely unsuccessful.

Because the sarcoid granuloma resembles histologically tubercle and, in the late stages of sarcoidosis, tuberculosis may appear, has led some investigators to the opinion that the two are synonymous. However, Snapper points out that patients with diabetes mellitus, Hodgkin's disease and leprosy are also prone to develop tuberculosis yet they are not caused by the same agent. Of particular significance from a clinical standpoint is the fact that sarcoidosis has a predilection for organs and tissues which are seldom the seat of tuberculosis, viz., skin, eyes, salivary glands, cranial nerves, pituitary body, myocardium, phalanges and bone marrow. On the other hand, the

serous membranes, which are often involved in tuberculosis, are comparatively immune to sarcoidosis Pleural effusion is seldom seen in sarcoidosis unless the disease is complicated by tuberculosis or heart failure Inclusion bodies are rarely, if ever, seen in tuberculosis

In addition to tuberculosis, several other possible etiologic agents have been suggested Tornell finds a close parallelism between sarcoidosis and pulmonary bronchomycoses, especially moniliasis This author therefore suspects a fungus as a possible cause Lofgren and Lundback were able to isolate a virus from every one of six cases of sarcoidosis investigated Preliminary tests showed that the virus probably belonged to the influenza-mumps Newcastle disease group of viruses Inasmuch as the disease has a predilection for the lungs eyes, tonsils and salivary glands, an inhalational infection is of course a possibility But it should be noted that when the lungs are involved in sarcoidosis the disease is invariably bilateral and symmetrical, a distribution that does not conform to aerogenous infection

Current opinion is veering to the view that sarcoidosis is a nonspecific disease probably of an allergic nature Suggestive indices, pointing to this concept are obtained in cases such as those reported by Bjerkelund also Myers and coworkers who described instances of sarcoidosis featured by migratory polyarthritis, erythema nodosum, fever and hilar adenopathy The response of sarcoidosis to ACTH and cortisone treatment, although often temporary, is also significant Finally, a number of experimental observations, relating to altered immunologic reactions, are on record which bespeak a nonspecific disease related to sensitivity According to this concept Boeck's sarcoid is believed to be a syndrome resulting from the individual's peculiar reaction to various agents Refvem reported cases of quartz granuloma or quartz sarcoid, and of sarcoid formation around foreign bodies other than quartz in patients with sarcoidosis This investigator also draws attention to the nonspecificity of sarcoid tissue and "Schaumann bodies" as evidenced by the production of these features in animals as a hypersensitivity reaction to a non microbic antigen According to Refvem, the obtainment of a Kveim reaction, to be described later, indicates that in genuine sarcoidosis one is dealing with only one causative agent or a group of closely related agents

Diagnosis

Sarcoidosis comes into consideration in the differential diagnosis of practically every obscure disease to which the body may fall heir, including such heterogeneous conditions as ocular lesions, dispituitarism, cardiac disease, portal hypertension, pyloric stenosis and migratory polyarthritis The following remarks deal in a general way with the diagnosis of systemic sarcoidosis but more specifically with the intrathoracic manifestations Additional features relating to the latter will be described in relation to the several forms of the pulmonary disease It should be stated at the outset that inasmuch as the etiology of sarcoidosis is unknown, the diagnosis rests on indirect evidence, chiefly on the demonstration of sarcoid structures in lymph node, liver, bone marrow or other organs and on certain clinical, roentgenological and immunologic features to be discussed presently A diagnosis of sarcoidosis is made, not only on the basis of positive histological findings, but also by excluding conditions such as those mentioned previously which may produce sarcoid like granulomas The diagnosis of sarcoidosis rests on a composite of findings rather than on results of individual tests

Symptoms and Signs

In spite of a multiplicity of organ involvements, the symptoms and signs of systemic sarcoidosis seldom reflect the extent of the disease This applies especially to any pulmonary involvement which may be present *Massive sarcoidosis* may affect the mediastinal lymph nodes and pulmonary parenchyma without causing any localizing symptoms or signs Low grade fever, malaise, weakness and loss of weight are often encountered On physical examination one may find enlarged peripheral lymph nodes, splenomegaly and skin lesions but often these are lacking Several syndromes of sarcoidosis present distinguishing composite features

Heerfordt's disease or uveoparotid fever is characterized by inflammatory lesions of the uveal tract of the eye painless swelling of the parotid glands and prolonged low grade relapsing fever Uveoparotitis is probably a variety of Mickulicz syndrome to be discussed later both manifestations of systemic sarcoidosis In the years prior to the recognition of Boeck's sarcoid as a systemic disease and before the widespread use of chest x rays only the visible lesions of sarcoidosis were recognized and a tuberculous etiology of the disease seemed quite plausible In recent years however the frequent demonstration of accompanying pulmonary and hilar lymph node involvement the absence of caseation and the failure to demonstrate tubercle bacilli in the lesions as well as other stigmata of sarcoidosis have served to relegate tuberculosis to the background The incidence of ocular sarcoidosis depends largely on the material studied Woods and Guyton ophthalmologists estimate that somewhere between 5 and 10 per cent of uveitis is due to sarcoid and that almost 50 per cent of sarcoid patients show ocular lesions Systemic sarcoidosis with major involvement in the lungs and hilar lymph nodes is only occasionally associated with ocular lesions

In 1941 Williams investigated forty cases of chronic irido cyclitis In twenty four chest positive x rays were obtained including twelve cases with diffuse miliary and reticular pulmonary changes two with massive mediastinal and hilar lymph node enlargement without pulmonary changes six with active chronic pulmonary tuberculosis and four with old healed fibrotic or calcific presumably tuberculous pulmonary foci Williams noted that although the extent of the pulmonary lesions in the patients with active pulmonary tuberculosis was considerable the general condition of the patients was surprisingly good Although Williams refers to my study on chronic hematogenous tuberculosis in the adult published in 1939 to help support his thesis that his cases were examples of chronic miliary tuberculosis I must confess that my conclusions were incorrect and that much of the material in my study and probably most of the cases cited by Williams represented systemic sarcoidosis

Mikulicz syndrome is characterized by symmetrical enlargement of the salivary and lacrimal glands Mikulicz concluded that the tissue changes represented those of a lymphosarcoma The symptom complex may be due to a distinct disease without associated lesions or it may occur as a syndrome in association with lymphosarcoma leukemia lead and other toxic agents as well as in sarcoidosis with uveal tract involvement

Case 26 Female—Age 21

The patient grava 3 para 2 registered at the Morrisania City Hospital Prenatal Clinic in the second month of her pregnancy A routine prenatal chest x ray on August 3 1948 in the third month of her pregnancy revealed bilateral hilar lymph node enlargement The patient was asked to return for further study but by the time she appeared two months later she had developed painless swellings of the parotid and lacrimal glands (Figure 40A)

On admission to the hospital the physical examination disclosed a well nourished female in no obvious discomfort Both parotid glands were swollen the left larger than the right The lacrimal glands were enlarged but not tender There was no palpable adenopathy anywhere else in the body The breasts were soft and contained no masses The lungs were clear to percussion and auscultation The heart revealed nothing abnormal The liver and spleen could not be felt The skin over the extensor surface of both legs were studded with lichenoid papules, pinkish in color Neurological examination showed a mild right facial weakness and left trigeminal hypalgesia

Repeated x rays of the chest revealed the same degree of enlargement of the hilar lymph nodes as noted in the initial film (Figure 40B) Roentgenograms of the hands and feet sella turcica and Stenson's duct revealed no abnormalities Numerous examinations of the sputum failed to reveal acid fast organisms The patient did not react to tuberculin in concentrations up to 1 0 mg intracutaneously The results of some of the other laboratory examinations were as follows Electrocardiogram of the heart was within normal limits Mazzini was negative The urinalysis was normal The white blood cell count was 4 900 per cu mm with 64 per cent polymorphonuclear cells 3 per cent lymphocytes and 4 per cent monocytes The

red blood cell count was 3 720 000 and hemoglobin was 11 gm ESR—18 millimeters in thirty minutes Total protein was 5 2 gm albumin 4 1 globulin 1 1, calcium 9 6 mg, phosphorus 2 5 mg and alkaline phosphatase 4 1 KA units Uric acid was 2 3 mg and urea nitrogen was 7 mg per cc Cholesterol was 363 mg per 100 cc and esters 168

An aspiration biopsy of the right parotid gland showed round cell infiltration on microscopic examination A skin biopsy of one of the papules showed some areas in the corium suggestive of epithelioid tubercles but these were not sufficiently characteristic to make a precise diagnosis The patient remained afebrile and asymptomatic After a stay of five weeks at the hospital she was discharged and followed in the Chest and Prenatal Clinics By January 1949 the swelling of the parotid glands had decreased considerably but the condition of the lacrimal glands remained unchanged

On February 5 1949 the patient was admitted to the hospital in active labor A transverse presentation was encountered The fetal heart was good but disappeared as labor progressed A version and extraction of a stillborn male child was done Autopsy of the fetus revealed atelectasis of both lungs cerebral edema and minute cerebral hemorrhages The diagnosis was asphyxiation There was no evidence of sarcoidosis or tuberculosis The mother's postpartum course was uneventful

In March 1949 the patient returned to the Chest Clinic complaining of pain in the left breast Examination revealed a plum sized mass in the left upper quadrant A biopsy of this mass showed hyperplastic breast acini and ducts with many small tubercles consisting of epithelioid cells connective tissue and giant cells but no caseation The diagnosis was sarcoidosis Follow-up examinations revealed no significant changes in the chest x ray findings The swelling of the parotid glands in time subsided but the right lacrimal gland enlargement was still present when the patient was last seen

It may be pertinent, at this point, to cite another experience with sarcoidosis complicated by pregnancy with a happier outcome A Negro woman of twenty three had given birth to a healthy child at the Morrisania City Hospital five months previously As a result of a routine chest x ray taken elsewhere, the patient was referred to the Chest Clinic with a diagnosis of miliary tuberculosis The patient had practically no symptoms or signs referable to the chest Chest x rays revealed nodular and reticular infiltrations throughout both lungs (Figure 43A) A palpable lymph node was found in the left epitrochlear region which was excised and histologic examination showed many epithelioid tubercles containing occasional Langhans giant cells with a surrounding zone of lymphocytes There was no caseation The diagnosis was sarcoidosis Repeated examination of the sputum failed to reveal



Figure 40 Case 26 Sarcoidosis associated with Mikulicz syndrome A (*Left*) Enlarged parotid glands swelling of right lacrymal gland B (*Right*) Chest x ray (early in pregnancy) shows bilateral prominent hilar densities (Biopsy of breast tissue nodule also of skin revealed changes consistent with sarcoidosis stillborn at term)

acid fast bacilli The tuberculin reaction was negative in concentrations up to 1 0 mg The patient was allowed to go to term and delivered a healthy child Two years later, the patient delivered another healthy infant In the meantime, the disease in the lungs had undergone spontaneous regression (Figure 43B) A report of this and the preceding case, by Ayvkan and Juskowitz in 1950, was the first one published on the association of sarcoidosis and pregnancy I have since followed the course of a third patient with sarcoidosis who went through pregnancy successfully

Jungling's disease is characterized by cystic changes in small bones which appear roentgenologically as circumscribed areas of rarefaction or, more often, as a reticulated or "lace like" pattern or a combination of both The phalanges, metacarpals and metatarsals are most often involved, but the nasal bones humerus, ulna, femur and tibia may also be affected (Figure 41B) There is usually little, if any joint involvement so that in spite of advanced degrees of bone destruction, the motion of the parts is maintained With few exceptions, the cystic changes in the small bones are found in association with stigmata of sarcoidosis in other parts of the body Sarcoidosis of small bones has to be differentiated from multiple cystic tuberculosis an extremely rare occurrence The earlier literature on the subject assumed the osseous changes to be caused by the tubercle bacillus, hence the term originally applied by Jungling to this syndrome, "ostitis tuberculosa multiplex cystica"

If one reviews the reported cases of Jungling's disease, one is impressed with the considerable number of children who had negative tuberculin skin reactions and negative guinea pig inoculations The hilar adenopathy ascribed to childhood tuberculosis was due in most instances to sarcoidosis Holt and Owens credit Kienbock with the first description of the bone lesions of sarcoidosis, published in 1902 Jungling was among the first to establish histologic proof that the lesions in the bones were due to a granulomatous process identical microscopically to the changes described by Boeck Of sixty-five patients with generalized sarcoidosis reported by Holt and Owens, only eleven, or 16 per cent, had definite bone lesions An almost identical percentage (17 4) of bone lesions was found by Ricker and Clark Significantly, higher percentages of osseous lesions have been reported from European countries

A *Banti like syndrome* may be encountered on rare occasions when systemic sarcoidosis is associated with massive enlargement of the liver and spleen and an accompanying ascites Several reports are on record of patients in whom splenectomy was done in the mistaken belief that the condition was Banti's syndrome Nordland and co-workers reported the case of a twenty-six year old pregnant woman with thrombocytopenic purpura Splenectomy was successfully performed in the fifth month of pregnancy Examination of the extirpated spleen showed sarcoidosis The pregnancy terminated normally at term It should be mentioned that Banti's syndrome is such an ill-defined entity that sarcoidosis or any other disease of the liver associated with anemia leukopenia, splenomegaly and portal hypertension is included in the syndrome Mino and co workers reported a case of manifest systemic sarcoidosis with marked hepatosplenomegaly and ascites After splenectomy and splenorenal venous anastomosis, the patient experienced considerable symptomatic relief of the ascites, dyspnea and abdominal discomfort An analogous experience was cited by Dunlap and coworkers These investigators reported the case of a pregnant woman with portal hypertension that was apparently produced by sarcoidosis involving the liver and spleen The patient underwent splenectomy, an end to side splenorenal shunt and five and one half months later delivered a normal baby at home

Case 27 Female—Age 36

A colored female was admitted to a hospital complaining of cough fever, weakness, shortness of breath and loss of twenty-five pounds in weight More recently, the patient had noted swelling and pain of the abdomen, nausea and vomiting after meals The immediate cause of the patient's seeking hospital treatment was bleeding from the gums This had lasted seven hours The past personal and family histories were irrelevant except for the fact

that two years previously the patient had a seizure of painful swelling of joints and fever The condition was diagnosed as rheumatic fever and the patient was hospitalized for twenty five days On the basis of the chest x ray findings also a biopsy of an epitrochlear lymph node a diagnosis of tuberculosis was made and the patient was treated with streptomycin and isoniazid for a period of twenty five days until she was transferred to Seton Hospital

At Seton Hospital it was soon apparent that one was dealing with systemic sarcoidosis The chest x rays revealed bilateral hilar lymph node enlargement and fine reticular striations extending into the midportions of both lungs (Figure 41A) In addition the left scapula showed a punched out cystic area Repeated examinations of the sputum and gastric contents failed to reveal acid fast organisms The tuberculin reaction was negative in all strengths A review of the biopsy of the epitrochlear lymph node revealed noncaseating epithelioid tubercles with Langhans giant cells some of which contained asteroid inclusion bodies Of particular interest from the viewpoint of the present discussion was the finding of an enlarged liver which was palpable four fingerbreadths below the right costal margin also a greatly enlarged spleen which occupied the entire left upper quadrant The presence of secondary anemia and other laboratory tests were in keeping with a Banti like syndrome due to sarcoidosis

Tuberculin Reaction

Approximately two thirds of patients with sarcoidosis fail to react to tuberculin or react weakly to concentrations as high as 1 0 mg or more Several theories have been proposed in explanation Physicians who do not subscribe to the belief that sarcoidosis is causally related to tuberculosis, and these are in the majority, draw the obvious conclusion that a negative tuberculin

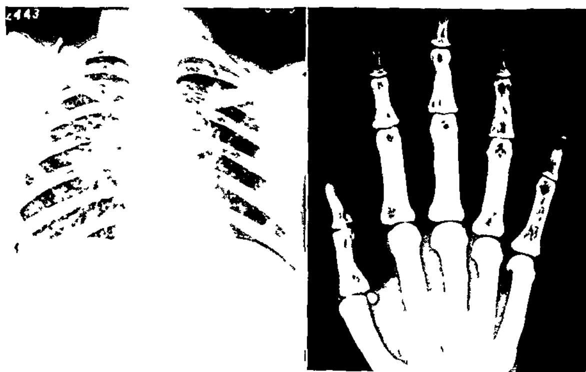


Figure 41 Case 27 Sarcoidosis associated with a Banti like syndrome A (*Left*) Enlarged hilar lymph nodes irregular reticular infiltrations permeating both lung fields cystic area in left scapula (Biopsy of lymph node revealed changes consistent with sarco dosis)

Sarcoidosis associated with Jungling s disease B (*Right*) Phalanges show circumscribed areas of rarefaction (in a patient with proved systemic sarcoidosis)

speaks against tuberculosis On the other hand those who believe that sarcoidosis and tuberculosis are different facets of the same disease ascribe the lack of reactivity to tuberculin to positive anergy a questionable state

In the differential diagnosis a negative tuberculin test is of considerable value providing it is in keeping with other clinical and laboratory findings It is well known that in moribund states and during intercurrent illnesses the tuberculin reaction may be depressed This applies also to Hodgkin s disease and mycosis fungoides As a matter of interest rather than one which sheds any light on the subject it may be mentioned that Lemming was able to produce cutaneous sarcoid lesions by injecting BCG vaccine in a patient with sarcoidosis Billings and Shapiro document the case of a white female with papular skin lesions of a typically sarcoid like nature A biopsy specimen was obtained and at the same time old tuberculin 001 mgm was injected in another site A positive tuberculin skin reaction was obtained Approximately a month later another biopsy of a similar papular lesion as well as one taken from the site of the tuberculin injection revealed sarcoid like lesions in both Obviously there are many unexplained phenomena associated with sarcoidosis

Michael and co workers found a significantly higher prevalence of tuberculin nonreactors in sarcoidosis in rural areas where negative tuberculins are commonly encountered These investigators believe that possibly the etiologic agent of the disease may be more heavily concentrated in these areas It may also explain the higher percentage of sarcoidosis in Negroes born in the Southern rural regions of the United States But the waxing and waning of the tuberculin skin reaction as may be encountered in sarcoidosis indicates a more profound disturbance Furthermore the allergic state as expressed in the skin and represented in the tuberculin reaction does not necessarily reflect the allergic state of other organs or the body In a study of BCG vaccination in twenty patients with sarcoidosis Israel and co workers found that sarcoidosis patients were unable to develop and maintain skin sensitivity to tuberculin

The tuberculin anergy in patients with sarcoidosis appears to be nonspecific due to interference with general immunologic mechanisms and does not establish sarcoidosis as an anergic form of tuberculosis In keeping with this concept Friou found that patients with sarcoidosis showed a depression of activity to extracts of mumps virus *Candida albicans* and *Trichophyton gypseum* This depression was greatest in sarcoid patients with negative tuberculin reactions The results of these tests seem to fit with the belief that sarcoid patients suppress delayed cutaneous reactions to all antigens Sones and Israel also found that patients with sarcoidosis react significantly less often than do control to tuberculin pertussis agglutinogen mumps virus and Oidiomycin Hence they conclude the relative anergy to tuberculin accompanying sarcoidosis is nonspecific

Laboratory Findings

There are few adequate studies available of the blood chemistry of large groups of patients with sarcoidosis during the prolonged course of the illness Some of the reported results based on studies of small numbers of patients are even contradictory possibly because single examinations are made of different forms or stages of the disease It may be stated categorically that if laboratory findings are in keeping with the clinical findings they are helpful in diagnosis in themselves laboratory tests are of little value

As might be expected of a disease with a predilection for the reticuloendothelial system active sarcoidosis is associated with an elevation of the globulin fraction of the blood chiefly of the gamma fraction with a resulting increase in the total serum proteins A reversed A G ratio may be present even if the total serum proteins are within normal limits as is often the case With subsidence of active disease the A G ratio tends to return to normal values although the A G ratio and the clinical activity do not necessarily parallel Since there are comparatively few conditions (lymphopathia venerum lupus erythematosus certain liver diseases multiple myeloma and Kala Azar) which are characterized by a reversal of the A G ratio its occurrence in sar

coidosis is of diagnostic value The diagnostic significance of other blood chemical values is debatable

There is often an elevated serum calcium and usually a normal serum phosphorus unless there are associated renal lesions The alkaline serum phosphatase may also be raised if there is significant liver damage more often it is within normal limits In the presence of hypercalcemia one may find nephrocalcinosis and/or nephrolithiasis also soft tissue calcifications The calcified foci may be present in the sarcoid lesions more often they are metastatic and not associated with bone disease Klatskin and Gordon described two cases of sarcoidosis with hypercalcemia metastatic calcification in one and renal stones in the other both associated with renal failure

A number of investigators have pointed out that sarcoidosis with hypercalcemia and associated metastatic calcification may be mistaken for hyperparathyroidism Distinguishing features of hyperparathyroidism are found in the generalized decalcification of bones rather than in the localized foci of sarcoidosis The raised alkaline phosphatase and the normal or low serum proteins are also in keeping with the former The calcium and phosphorus levels are not dependable in differential diagnosis It is well to point out that in spite of the frequent involvement of the kidneys with sarcoidosis renal failure is rare I encountered one such case but at autopsy the cause of the azotemia and renal failure was found to be due to a polycystic kidney with double ureters and minimal sarcoid involvement

The blood cytology in sarcoidosis is not distinctive The erythrocyte sedimentation velocity is increased during the active phase and may or may not approach normal values with subsidence of the disease The leukocyte count is often within normal range at times slightly above occasionally below normal except during intercurrent febrile episodes when a leukocytosis is usually present Although a moderate degree of eosinophilia is common its absence is of little diagnostic value

Tissue Examination

Histologic study of tissues of patients suspected of having sarcoidosis is an important feature in the diagnosis of the disease But as mentioned the mere demonstration of sarcoid like granulomas is not sufficient to diagnose systemic sarcoidosis unless confirmed by clinical and roentgenological findings In fact a presumptive diagnosis of sarcoidosis can be made with a reasonable degree of accuracy on the basis of significant clinical and roentgenological findings even if a confirmatory biopsy is not available The most likely sites for the obtainment of biopsy specimens are the skin lymph nodes and liver An epitrochlear lymph node is frequently available for biopsy Other organs and tissues which may be used for biopsy are the uveal tract salivary glands tonsils and bone marrow It may be advisable at times to explore surgically the root of the neck on the right side to obtain lymph tissue in the paratracheal region occasionally one may have to resort to a biopsy of lung tissue The concluding section deals at greater length with the place of biopsies in the differential diagnosis of sarcoidosis and other obscure systemic diseases with pulmonary lesions

In the absence of easily available tissue needle biopsy of the liver an organ frequently involved in sarcoidosis is an additional means of obtaining material for histological study Before liver puncture is done the bleeding coagulation and prothrombin time are tested and other precautions taken Van Buchem performed liver biopsies on fourteen patients with sarcoidosis In eleven a positive biopsy was obtained Of three with negative biopsies two had arrested disease and the third typical skin lesions Klatskin and Yesner performed liver biopsies in twenty cases of sarcoidosis They were able to demonstrate submiliary granulomata in fifteen histologically confirmed cases but in none of five with only a presumptive diagnosis In ten of the former the histological confirmation of the diagnosis rested on the liver biopsy findings alone These investigators point out that submiliary granulomata in the liver are also demonstrable by needle biopsy in miliary pulmonary and osseous tuberculosis in erythema nodosum and in brucellosis Smaller somewhat atypical granulomata are demonstrable in infectious mononucleosis influenza B in

certain infections and in actinomycosis The authors cite others who found such granulomata in early syphilis leprosy tularemia and mycotic infections

Kveim Reaction

An intracutaneous injection of saline suspension of lymph node or other tissue obtained from a patient with active sarcoidosis produces a nodule in certain recipients which on histological examination duplicates closely the structure of the sarcoid tubercle Originally described by Williams and Nickerson in 1935 the test was reintroduced and popularized by Kveim in 1941 The latter unlike his predecessors recognized the fact that it is a delayed reaction and that it takes several weeks often several months for sarcoid like tubercles to develop Lesions developing at the site of injection and showing typical papules have been reported as positive Kveim reactions as la e as one to five years after injection The Kveim reaction is specific insofar as patients with active sarcoidosis with few exceptions develop sarcoid like tubercles But the test is not a specific one since it may follow intracutaneous injection of suspensions of normal human spleen killed as well as living tubercle bacilli silica containing material and other substances Danbolt considers the Kveim *reaction an allergic phenomenon* suspensions of sarcoid tissue presumably containing unknown specific substances which *are responsible for the development of the skin* reaction There are a number of reasons however why the *Kveim test cannot* be considered an allergic reaction one being the long latent period which may elapse before a positive test is obtained

As mentioned the Kveim reaction is associated with a high percentage of positive results in patients with active sarcoidosis but in a small percentage false positive reactions are also obtained Siltzbach and Ehrlich performed *571 Kveim tests* in 200 patients A positive reaction characterized by the production of tuberculoid granulomas resembling those of sarcoidosis was obtained in 86 per cent of patients with biopsy confirmed sarcoidosis False positive results were obtained in only 4 per cent It should be noted however that among a comparable group of patients strongly suspected of having sarcoidosis on clinical grounds alone and without biopsy confirmation the authors *also obtained positive Kveim* tests in 85 per cent In other words the Kveim reaction is not essential for making a diagnosis In fact Israel and Sones obtained positive Kveim tests in 42 4 per cent of thirty three patients with tuberculosis *and in 8 3 per cent of other control* subjects Surprisingly they obtained positive Kveim tests in only 71 1 per cent of patients with sarcoidosis Contrary to the experience of most investigators Israel and Sones were unable to confirm the diagnostic value of the Kveim test

Rogers and Haserick tested 103 patients with Kveim antigen Of fifty one patients with clinically active sarcoidosis only two had negative tests Six patients with sarcoidosis in clinical remission also gave negative tests A control group of forty two patients with other diseases including tuberculosis and beryllosis also gave negative tests These investigators studied the pathogenesis of the positive Kveim test by comparing positive tests of the same and different durations and by serial biopsy They concluded that the test is both reliable and practical in the diagnosis of sarcoidosis They suspect that the disease involves an antigen antibody mechanism produced by a tuberculoid stimulating agent

A unique experience is cited by Rogers and Netherton of identical twins who developed sar*coidosis In addition to other similarities* it was noted that in one patient the growth of the papule at the site of injection of the Kveim antigen seemed to parallel the clinical course of the disease After decreasing in size coincident with the clinical and chest x ray findings the papule grew in size with recurrence of the disease The lesion was excised about two and one *half years after the initial injection of the* Kveim antigen and on histological examination the tissue revealed characteristic focal collections of epithelioid cells and giant cells typical of sarcoidosis There is still much to be learned about sarcoidosis

Intrathoracic Sarcoidosis

Clinical Features

Sarcoidosis of the lungs and hilar lymph nodes

is accompanied by so few symptoms that patients seldom seek medical attention because of complaints referable to the chest If symptoms relating to the latter are present, they are apt to be caused by incidental factors rather than by the disease per se Considerable cough and expectoration, occasionally hemoptysis and fever, herald superimposed infection Increasing dyspnea orthopnea and edema indicate the development of chronic cor pulmonale

More often the physician is consulted because of the patient s general malaise and recurring fever or because of gross involvements of the skin, eyes, salivary glands or because of visibly enlarged lymph nodes In many, sarcoidosis is discovered in the course of routine chest x-ray examinations Schonholzer, in a chest x ray survey of 516,879 Swiss soldiers, found sixty-seven cases of pulmonary sarcoidosis, an incidence of 0 13 per cent The incidence of pulmonary involvement in systemic sarcoidosis varies according to the nature of the material studied and the particular interests of the examiner Ricker and Clark found evidence of pulmonary involvement in 36 per cent of 300 cases of sarcoidosis proved histologically by biopsy or autopsy Fisher (quoted by Woods) found pulmonary or mediastinal lymph node involvement in 83 per cent of 94 carefully studied cases

Roentgenology

Intrathoracic sarcoidosis presents roentgenologically such diversified appearances that the differential diagnosis takes in a large number of diseases which may affect the lungs and/or hilar lymph nodes From a study of a sizable number of cases of sarcoidosis, one may distinguish three broad roentgenologic patterns of the disease, one often merging with the other

A *hilar* form is characterized by bilateral hilar lymph node enlargement (Figure 40B) At times (Figure 45B), the tumefactions are massive and assume a "potato" like configuration At this stage, the disease is apt to be mistaken for a malignant lymphoma It is not improbable that of the histologically unproved cases of Hodgkin s disease or lymphosarcoma "cured" by one means or another, many represent spontaneously regressing sarcoidosis of the hilar lymph nodes

A *transitional* form, consisting of enlarged hilar lymph nodes plus parenchymal involvement, is probably the most frequent one encountered (Figure 41A) At this stage, sarcoidosis may simulate lymphangitic carcinomatosis, pneumonoconiosis as well as malignant lymphomas

A *parenchymal* form of the disease, usually but not necessarily associated with some degree of hilar lymphadenopathy, may assume an appearance of miliary nodules (Figures 42A and B), reticular striations (Figure 43A), diffuse interstitial fibrosis, focal fibrosis and emphysema (Figures 44A and B) or scattered rounded densities The differential diagnosis includes tuberculosis, fungus infections, dust inhalational diseases, berylliosis, lymphangitic carcinomatosis and metastatic neoplasms, among a number of other conditions

Intrathoracic sarcoidosis often undergoes spontaneous resolution, as far as can be judged roentgenologically, but the exact incidence of this outcome has not been established (Figures 45A, B and C) Spontaneous regression may take a few weeks or several years In a variable number, sarcoidosis, after developing to a certain stage, becomes arrested and, in time, assumes the picture of a diffusely fibrosing disease with emphysema Examination of such a lung may not provide any histologic evidence of sarcoidosis although the initial phases of the disease may have been featured by classical symptoms, signs and laboratory findings The disease may remain in a stage of arrest for many years Danbolt described the findings in the first case of the disease reported by Boeck forty one years earlier

In a certain percentage of cases the disease, usually in the advanced stages is complicated by superimposed tuberculosis A pleural effusion may then make its appearance Uncomplicated intrathoracic sarcoidosis is rarely associated with a pleural effusion, rather unusual of a disease which is believed to be allergic in nature Sarcoidosis of the lungs, associated with progressive fibrosis and emphysema, by causing increasing interference with the lesser circulation, leads in some cases to chronic cor pulmonale A coexist-

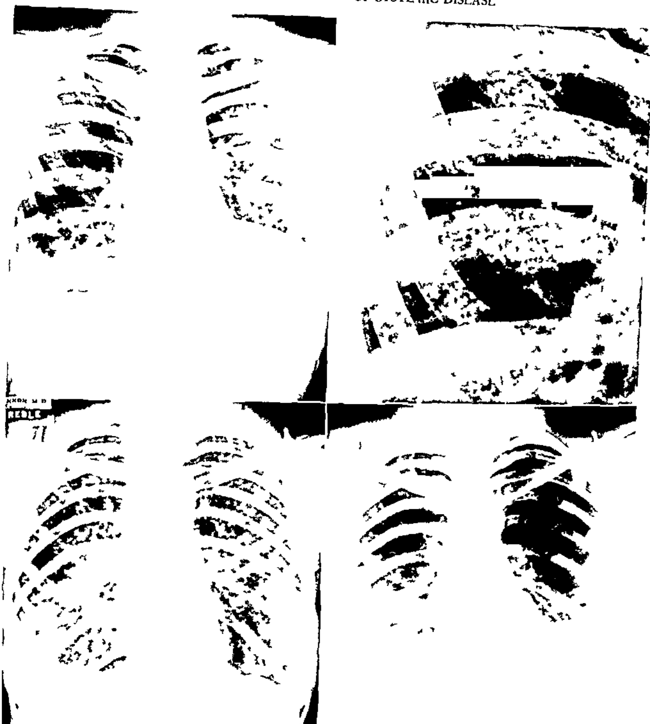


Figure 42 Sarcoidosis miliary type A (*Upper left*) Minute infiltrations involving both lungs B (*Upper right*) Detail showing foci and reticulations (Disease discovered accidentally chest x rays unchanged over a period of eight years no symptoms or signs referable to chest biopsy of lymph node tuberculin and other tests in keeping with sarcoidosis)

Figure 43 Sarcoidosis nodular type A (*Lower left*) Nodular and reticular infiltrations seeding both lungs enlarged right paratracheal lymph nodes (Biopsy of lymph node revealed tissue changes consistent with sarcoidosis) B (*Lower right*) Four years later clearing of infiltrations and regression of paratracheal lymph nodes. (In the interim patient bore two healthy children)

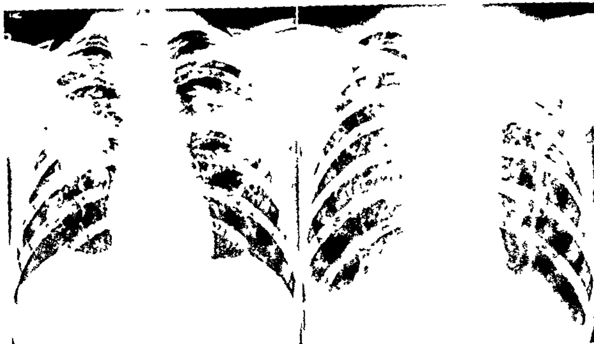


Figure 44 Sarcoidosis parenchymal form A (*Left*) Irregular, dense infiltrations in both upper lobes apical and basal regions hyperilluminated (Admitted to sanatorium with diagnosis of pulmonary tuberculosis) B (*Right*) Nine years later marked fibrosis of upper lobes and emphysema of remainder (Biopsy of lymph node early in disease revealed sarcoidosis died of chronic cor pulmonale autopsy showed intense fibrosis and nodularity of lungs no evidence of caseation no acid fast bacilli in tissues hypertrophy of right ventricle)

ing sarcoidosis of the heart may be a contributing factor

Treatment

There is no specific remedy for sarcoidosis because the etiology of the condition is unknown and the effects of treatment cannot be assessed since the disease is often self limited Among the many therapeutic measures which have been utilized a combination of streptomycin and cortisone appears most promising at the time of this writing

Streptomycin was initially used alone on the premise that sarcoidosis may represent an atypical form of tuberculosis But the results were not impressive excepting in cases with manifest tuberculosis complicating sarcoidosis Following observations on the effect of ACTH on certain inflammatory diseases of the eyes Sones and coworkers tested the effect of cortisone in two cases of widespread sarcoidosis The administration of cortisone, in doses of 100 mgs twice daily was followed by marked amelioration of symptoms The clinical improvement was paralleled by changes in the tissues obtained by biopsy after treatment The regression of the disease appeared to be at a faster rate than that observed in cases undergoing spontaneous healing

Subsequent reports by Lovelock and Stone, Small and others confirmed the immediate beneficial effects of cortisone on sarcoidosis, serial chest x rays showing not only decided clearing of the pulmonary lesions but improvement in function as well Somewhat disappointing results were obtained by Michael in ten patients with sarcoidosis treated with cortisone Like others he found cortisone to cause amelioration of symptoms but this did not seem to alter the basic course of the disease After the discontinuance of medication the lesions resumed their original state This phenomenon has since been confirmed by others (Figures 46 A, B C and D) Furthermore, in one instance reported by Small where a patient had received cortisone daily for

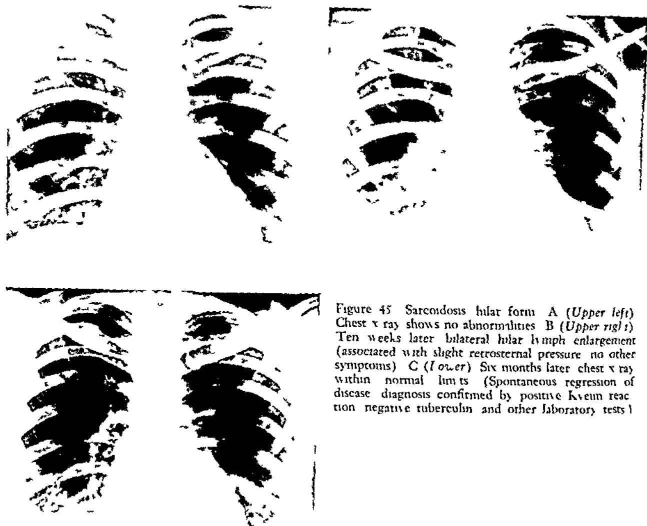


Figure 45 Sarcoidosis hilar form A (*Upper left*) Chest x ray shows no abnormalities B (*Upper right*) Ten weeks later bilateral hilar lymph enlargement (associated with slight retrosternal pressure no other symptoms) C (*Lower*) Six months later chest x ray within normal limits (Spontaneous regression of disease diagnosis confirmed by positive Kveim reaction negative tuberculin and other laboratory tests)

forty five days tuberculosis developed in the spine and urogenital tract The hazard of the administration of ACTH and cortisone to patients with latent tuberculosis is now recognized Controlled studies on the experimental animal parallel the observations in man

Israel and co workers recently reported their experience with thirty six cases of sarcoidosis treated with cortisone They found that benefit was most striking in patients with extrapulmonary lesions in the eyes parotid glands skin or heart and most marked in patients with recent disease However improvement in the pulmonary lesions was less frequently observed and no effect was noted on mediastinal lymphadenopathy Definite improvement occurred in 50 per cent of patients with pulmonary infiltrations in a few instances there was complete resolution These investigators did not encounter any instances of tuberculosis The failure to observe febrile relapses during or after cortisone treatment seemed sufficiently impressive to lead these investigators to conclude that sarcoidosis was probably not caused by an infectious agent Four patients died of progressive sarcoidosis who could not tolerate discontinuance of therapy

Hoyle and co workers analyzed the reported results of treatment of pulmonary sarcoidosis

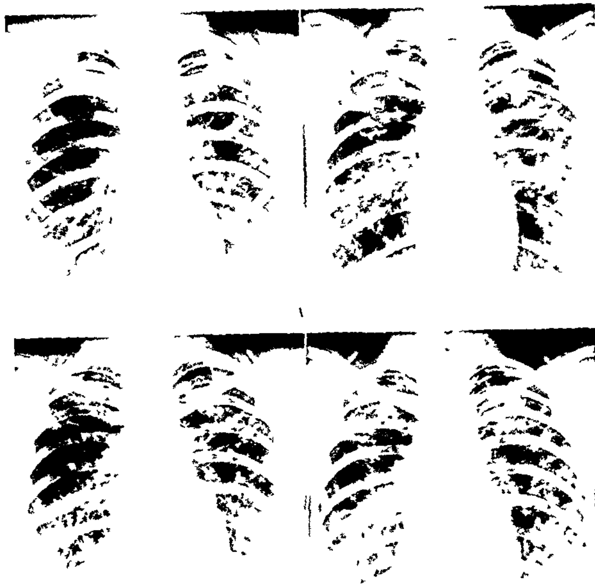


Figure 46 Sarcoidosis temporary improvement under cortisone treatment A (*Upper left*) Faint reticular infiltrations more marked in left lung B (*Upper right*) Five years later patchy infiltrations *involving both* lungs (simulating metastatic neoplasm) C (*Lower left*) After four months cortisone treatment moderate degree of regression of infiltrations D (*Lower right*) Five months after discontinuance of cortisone infiltrations more extensive than before treatment (Course of disease featured by a minimum of symptoms and physical signs Reinstitution of steroid treatment was again followed by regression of infiltrations)

with cortisone or ACTH On the basis of a radiological assessment of eighty nine cases, sixty-five showed improvement after three months of treatment However, partial relapse occurred in eleven and complete relapse in twenty six The percentage of those who maintained their improvement corresponds roughly with that obtained by Israel and co workers On the basis of an original study of thirty eight patients with pulmonary sarcoidosis, of which thirty were treated with streptomycin plus para aminosalicylic acid (PAS) and with cortisone plus streptomycin and PAS Hoyle and co workers found that the latter combination was much superior They also noted that the improvement was more frequent and more complete among the patients with recent disease They found it safe to combine the treatment up to a year Unfortunately, it was difficult to decide when the treatment should be given, as many others have found and when it should be stopped One must conclude, therefore, that although a trial of cortisone or ACTH, preferably in combination with streptomycin and PAS, is indicated in acute forms of sarcoidosis, the benefit to be derived from treatment of chronic forms of the disease, especially sarcoidosis of the lungs, is problematic In any event, one has to be on guard against untoward reactions which may arise as a result of sudden withdrawal of the hormone

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Chapter 10

Pulmonary Manifestations of Certain Abdominal and Metastatic Diseases

Pulmonary Manifestations of Abdominal Diseases

Introduction

An adequate description of the various abdominal conditions which may be associated with *pleuropulmonary manifestations* would involve a more elaborate discussion of the subject than can be accommodated within the scope of these pages. For the present purposes it will suffice merely to define the more important diseases. It should be stated at the outset that a complete examination of the thoraco abdominal region, as much of it as can be visualized in conventional chest roentgenography, utilizes fluoroscopy as well as chest x rays. The latter include exposures in expiration and inspiration. In obscure disease one has to examine the entire gastrointestinal tract, including the use of a barium enema. Occasionally the induction of a pneumoperitoneum is indicated and in particularly difficult situations, exploratory surgery.

Diseases originating in the abdominal cavity may be reflected in the thoracic cavity in one of several ways: (1) by the pressure exerted on the diaphragm and the resulting limitation of motion of the muscle thereby interfering with aeration of the lungs; (2) through localized bulgings of the diaphragm or herniation of abdominal viscera; (3) through the formation of a ...

event the presence of disease in the abdomen may be first evident above the level of the diaphragm and contrariwise the first inkling that all is not well below the diaphragm may first be apparent in a chest x ray.

In the course of routine chest roentgenography of newly admitted patients to general hospitals with a diagnosis of acute surgical abdomen, one may find occasionally collections of free air under one or both leaves of the diaphragm. The accidental discovery of escaped air under such circumstances indicates the presence of a perforated abdominal viscus. At other times one may find the diaphragm unduly elevated by gaseous distention of the bowel, the latter possibly showing fluid levels. These findings are in keeping with strangulation of the gut.

Kirklin and Gilbertson have drawn attention to the importance of inspecting the air filled upper segment of the stomach in reading chest x rays. The gas bubble at the cardiac end of the stomach is normally smooth and translucent. A mass projecting into the gas bubble may be clearly visible and the presence of tumor strongly suspected from the routine chest x ray examination alone (Figures 47A and B). Large neoplasms or infiltrative lesions may cause deformity of the fundus of the stomach or even complete obscuration of the gas bubble.

Diseases of the Diaphragmatic Region

Diaphragmatic Displacements

Diseases of the lungs and mediastinum may interfere with diaphragmatic activity as a result of fixation of the muscle by pleural adhesions or as a result of upward suction of the diaphragm

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On rare occasion, the diaphragm may be the site of a tumor originating in the muscle. The neoplasms most frequently encountered are lipomas and fibrosarcomas. Partial eventrations of the right leaf of the diaphragm causing localized bulging of the muscle are often seen (Figure 49A and B). Such circumscribed bulgings almost invariably affect the anteromedial portion of the diaphragm and may simulate tumor. Obvious intraabdominal conditions such as advanced pregnancy, ascites and abnormally enlarged viscera or tumor masses, which may cause diaphragmatic displacement, need only be mentioned.

An infrapulmonary collection of fluid, usually an empyema, may simulate an elevated diaphragm or a subphrenic abscess or tumor. If the involvement is on the left side, the presence of the stomach bubble or gas containing colon may permit a proper diagnosis. The stomach bubble may be accentuated by a carbonated drink before fluoroscopy. If the fluid is encapsulated beneath the right lung, the differential diagnosis between supra- and infradiaphragmatic disease is much more difficult. Thoracentesis may be unsuccessful because of the localized nature of the fluid, the encapsulation being caused by adhesions which anchor the lung to the diaphragm. Chest x-rays in lateral decubitus projections may also be unrevealing. Under such conditions, a diagnostic pneumoperitoneum is the best means of demarcating the position of the diaphragm and thereby localizing the fluid collection.

Eventration of the diaphragm is a developmental anomaly of the muscle affecting in most instances, the left leaf (Figure 48B). The highly placed diaphragm may or may not be associated with Kienbock phenomenon. Eventration should be differentiated from an abnormally elevated stomach due to a congenitally shortened esophagus. In case of the former, after a barium meal the radiopaque mass is visible at a higher plane than that of the esophageal opening. At this juncture, it might be profitable to mention the occasional encounter of pulmonary disease secondary to cardiospasm or mega-esophagus. As might be expected, the overflow of esophageal contents into the lungs is apt to cause aspiration



Figure 48. A (*Left*). Paralysis of left leaf of diaphragm caused by a bronchiogenic carcin[illegible] ading the phrenic nerve [illegible] laryngeal nerve [illegible] recurrent right. (Male ag[illegible] ed to the of re[illegible] History [illegible] and dizziness when lying on the left side.)

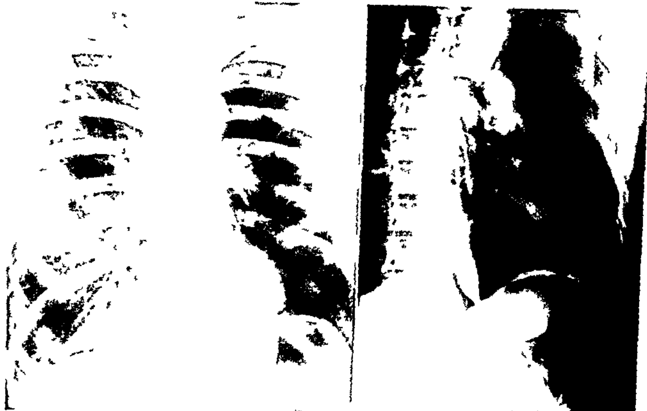


Figure 47 Carcinoma of stomach discovered accidentally in routine chest x ray A (*Left*) Rounded density at cardia of stomach B (*Right*) After barium meal mass is seen more clearly (At operation a carcinoma was found originating at lower end of esophagus protruding into stomach, subtotal gastrectomy and gastroesophagostomy)

by abnormally high negative intrapleural pressure Acute peritonitis pneumoperitoneum ascites and markedly enlarged abdominal viscera may likewise push the diaphragm upward and interfere with diaphragmatic motion The activity of the diaphragm may be hindered through actual disease of the muscle or as a result of reflex action initiated elsewhere It is noteworthy that the pressure immediately beneath the diaphragm fluctuates in the same direction as it does immediately above the muscle The equalized pressure of the thoraco abdominal region facilitates the return of blood to the right side of the heart but also acts adversely by aiding the transfer of free fluid and infectious elements through the diaphragm

Pleuropulmonary fibrosis with shrinkage of the intrathoracic contents is a frequent cause of retraction and upward displacement of the diaphragm The latter is also brought about by bronchial obstruction and pulmonary atelectasis

A reduction of activity of the diaphragm may be detected fluoroscopically by having the patient sniff or cough thereby inducing a jerky motion of the muscle Paralysis of the phrenic nerve by an invading malignant tumor is a common cause of diaphragmatic displacement (Figure 48A) It should be noted that phrenic nerve paralysis due to invading carcinoma need not necessarily be associated with a visible tumor mass The chest x ray may fail to show any abnormalities aside from the elevated diaphragm Occasionally both the phrenic and recurrent laryngeal nerves are compromised Early in the disease, the paralysis may be transient, with continued invasion the paralysis becomes permanent The highly placed diaphragm is usually associated with a paradoxic motion of the muscle the latter moving upward in inspiration and downward in expiration (Kienbock phenomenon) Aortic aneurysm may also cause phrenic nerve paralysis



←

(*See legend on opposite page.*)



Figure 49 Localized bulging of diaphragm simulating tumor A (*Left*) Rounded mass immediately above right leaf of the diaphragm B (*Right*) Lung detail (In the lateral projection the mass was situated anteriorly, to *the right of the sternum patient under observation for more than six years without change in configuration of the* mass, bronchoscopy and other studies negative for neoplasm)

pneumonia and suppuration (Figures 50A, B C and D) Prolonged low-grade infection results in a chronic nonspecific pneumonitis usually involving the right lower lobe Since mega-esophagus may be associated with few or insignificant symptoms, it is well to bear this condition in mind in the differential diagnosis of any obscure pulmonary disease with features of an aspiration infection

Herniation of the diaphragm may be developmental or acquired usually the former Developmental defects may vary from total absence of the muscle to circumscribed weaknesses which allow limited protrusions of abdominal contents Favorite sites of herniation are in the dorsolateral aspect of the diaphragm through the foramen of Bochdalek, or through the esophageal hiatus posteriorly or through the foramen of Morgagni, parasternally Hernias are termed false if they have no covering sac, in which case they are apt to allow free passage of multiple abdominal viscera The resulting pressure exerted on the heart and lungs often leads to early death unless the defect is corrected surgically Massive congenital hernias are almost invariably of the false type

Hiatus hernia is a common occurrence in elderly persons The condition often mimics acute coronary artery disease, paravertebral abscess mediastinal collections of fluid or neoplasms O Connor and Rivo draw attention to several features which may enable the physician

Figure 50 Mega esophagus complicated by aspiration pneumonia A (*Upper left*) Widening of superior mediastinum lung clear heart slightly enlarged B (*Upper right*) Irregular consolidation of right lower lung (associated with chill fever pain in chest and fetid sputum) C and D (*Lower left and right*) Esophagogram showing markedly dilated esophagus (History of recurring seizures of vomiting and pulmonary *infection*, partial improvement after passage of mercury weighted tube and antibiotics)

pleura is supplied by branches of the internal mammary and intercostal arteries tributaries of the subclavian arteries As a result inflammatory disease and circulatory disturbances may affect the pleural cavity by way of the greater circulation

What is particularly significant from the viewpoint of the present discussion is the fact that a sudden seizure of chest pain and fever the elicitation of a pleural friction rub and the appearance of fluid in the chest may indicate a systemic as well as a local source As has been repeatedly stressed in these pages involvement of the pleura may be the first manifestation of a systemic disease In any large collection of pleurisies of diverse origin a sizable number remain unexplained Many of the latter undoubtedly represent manifestations of systemic diseases which never come to light or appear at a later date in more definitive form A frequent cause of unexplained pleurisy with effusion in young persons is tuberculosis of the spine In older persons metastatic malignancy of the spine or of the ribs may be a cause

Pleurisies of whatever origin are usually associated with free fluid in one or both pleural cavities Initially it may be difficult to demonstrate a diaphragmatic pleurisy since as has been shown by a number of investigators the pleural cavity has to contain at least 300 cc of fluid before the collection becomes visible in the chest x ray With increasing size the fluid rises above the costophrenic sinus and is demonstrable roentgenologically The fluid soon rises upward and laterally along the costal margin in time displacing the heart and mediastinum to the contralateral side At times difficulties may be encountered in diagnosing an acute diaphragmatic pleurisy because the accompanying pain may be referred to the neck or abdomen In case of the

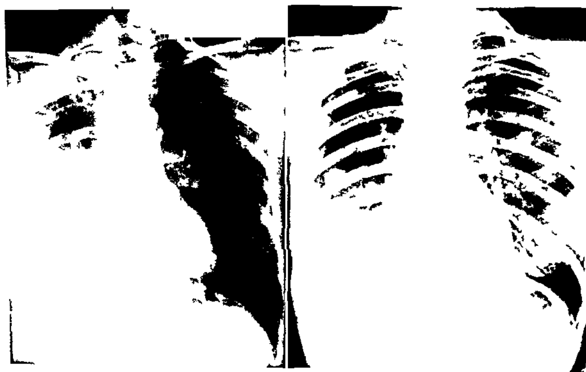


Figure 52 Pleural effusion as an early sign of metastatic carcinoma A (*Left*) Pleural effusion occupying lower half of right chest heart not displaced visible parenchyma not involved B (*Right*) Six years later several circumscribed densities are seen in both lungs pleuritis at right base (At this time symptoms appeared referable to the abdomen X rays of the gastrointestinal tract showed a mass at the rectosigmoid junction exploratory laparotomy revealed an inoperable carcinoma of colon)



Figure 51 Parasternal diaphragmatic hernia A (*Left*) Rounded edge of a density faintly seen at right cardio-diaphragmatic angle (Note absence of stomach bubble) B (*Right*) Barium meal shows stomach displaced to the right the barium occupying the density previously noted (In the right lateral projection the herniation was seen to be in the region of the foramen of Morgagni parasternally The patient a man of thirty had been treated for many years for unexplained anemia)

to suspect the presence of a hiatus in the routine chest x ray In the posteroanterior projection a small hiatus hernia is superimposed on the heart shadow slightly to the left of the lateral border of the spine The hernia appears as a rounded or ovoid shadow either of a soft appearance if filled with fluid or as a localized area of hyper illumination if filled with air In the lateral projection the hernia is found to be in back of the heart Of particular significance is the absence of the stomach gas bubble in the usual position due to displacement of the organ medially and upward in right sided parasternal diaphragmatic hernia (Figures 51A and B)

Opaque meal studies are essential to confirm the diagnosis of diaphragmatic hernia Since the stomach and colon including omentum are the most frequent organs displaced the examination of the barium filled gastrointestinal tract should include x ray exposures in the Trendelenburg as well as in conventional positions Jenkinson and Roberts estimated that only 5 per cent of hiatus hernias could be diagnosed if the erect position alone were used in the examination Among 3 448 patients examined in a two year period Brick found 308 hernias of the esophageal hiatus an incidence of 8 93 per cent This was the second most frequent lesion diagnosed duodenal ulcer being found in 20 41 per cent of the patients Hiatus hernia was more than twice as frequent as gastric ulcer or gastric carcinoma

Diaphragmatic Pleurisy

A pleurisy may be caused by a variety of agents including bacterial viral neoplastic and traumatic (Figures 52A and B) The pleura may be involved by extension of disease from the lungs lymph nodes spine pericardium or other structures within the chest from abdominal organs and from distant sites The blood supply of the pleura renders the membrane especially vulnerable to systemic disease The visceral pleura is supplied by capillaries derived from the bronchial arteries tributaries of the aorta the parietal

pleura is supplied by branches of the internal mammary and intercostal arteries tributaries of the subclavian arteries As a result inflammatory disease and circulatory disturbances may affect the pleural cavity by way of the greater circulation

What is particularly significant from the viewpoint of the present discussion is the fact that a sudden seizure of chest pain and fever the elicitation of a pleural friction rub and the appearance of fluid in the chest may indicate a systemic as well as a local source As has been repeatedly stressed in these pages involvement of the pleura may be the first manifestation of a systemic disease In any large collection of pleurisies of diverse origin a sizable number remain unexplained Many of the latter undoubtedly represent manifestations of systemic diseases which never come to light or appear at a later date in more definitive form A frequent cause of unexplained pleurisy with effusion in young persons is tuberculosis of the spine In older persons metastatic malignancy of the spine or of the ribs may be a cause

Pleurisies of whatever origin are usually associated with free fluid in one or both pleural cavities Initially it may be difficult to demonstrate a diaphragmatic pleurisy since as has been shown by a number of investigators the pleural cavity has to contain at least 300 cc of fluid before the collection becomes visible in the chest x ray With increasing size, the fluid rises above the costophrenic sinus and is demonstrable roentgenologically The fluid soon rises upward and laterally along the costal margin in time displacing the heart and mediastinum to the contralateral side At times difficulties may be encountered in diagnosing an acute diaphragmatic pleurisy because the accompanying pain may be referred to the neck or abdomen In case of the



Figure 52 Pleural effusion as an early sign of metastatic carcinoma A (*Left*) Pleural effusion occupying lower half of right chest heart not displaced visible parenchyma *not involved* B (*Right*) Six years later several circumscribed densities are seen in both lungs pleuritis at right base (At this time symptoms appeared referable to the abdomen X rays of the gastrointestinal tract showed a mass at the rectosigmoid junction exploratory laparotomy revealed an inoperable carcinoma of colon)

latter, the symptoms may simulate an acute surgical abdomen.[7]

Subphrenic Abscess

A purulent collection of fluid below the diaphragm seldom originates in the chest but signs of its presence are often first demonstrable above the diaphragm. In the majority of cases a subphrenic abscess results from extension of infection from the abdomen. Infection of the subphrenic spaces is aided by the normally negative pressure in this region, the rich lymphatic supply of the diaphragm favoring the transfer of infection to the pleural surface. A pleural effusion develops early with fixation and elevation of the *diaphragm on the affected side. The demonstra*tion of free air or a fluid level under the diaphragm, in a patient who had recently undergone an abdominal operation, points strongly to a subdiaphragmatic abscess.

The chest x-ray is also of inestimable value *in the detection of pleuropulmonary complica*tions, following abdominal operations. The incidence of atelectasis, pneumonia and pleural effusion is notoriously high after operations on the stomach, duodenum and biliary tract, especially in patients subject to bronchitis, emphysema or other conditions interfering with cough. This applies also to patients who have restrictive abdominal binders or are under excess sedation. The retained secretion in the smaller bronchi causes segmental atelectasis leading to bronchopneumonia. Even in the years when chest roentgenography was done only *after the appearance* of symptoms pointing to an intrathoracic complication following surgery, the incidence of postoperative pulmonary lesions was quite high. With increasing use of routine chest roentgenography, the incidence of demonstrable complications has been *shown to be considerably higher.*

Rudnikoff and Headland had chest x-rays taken of forty consecutive patients who were being prepared for cholecystectomy. Chest x-rays were repeated on the fourth postoperative day and at the time of the patient's discharge. "*Positive postoperative chest x-rays* were obtained in 28 to 70 per cent. In the majority, the chest x-ray findings were transitory but in seven there were residual lung lesions at the discharge. Atelectasis and bronchopr were most frequent. In many cases it possible to make a differential diagnosis exact nature of pleuropulmonary lesi ninety patients undergoing abdominal op Palmer and Sellick found atelectasis in cent. In a duplicate series of ninety pat whom certain preventive measures we tuted, the incidence *declined to 9 per c*

Diseases Involving Abdominal Vi

Clinical Features

There are a number of intraabdominal which may give evidence of their pres the chest. The frequent occurrence of nary infection and bronchiectasis in asso with cystic fibrosis of the pancreas has be cussed in Chapter 2. In considering the pulmonary manifestations of abdominal it is preferable to deal with the effects latter, as a group, rather than with ind conditions. The occurrence of linear hor striations in a chest x-ray, or the find patchy basal infiltrations or the detection appreciable amount of fluid in one or both cavities are phenomena which may be asso with any of the abdominal diseases lis Table 5. Weber and Gregg found that ulcer may be associated with chronic pulm disease, characterized by diffuse fibros emphysema. This association does not hol for duodenal ulcer. These investigators re a series of seventy cases of benign gastric in which chronic nonspecific pulmonary d coexisted in 43 per cent. The suggestion fered that some fundamental degenerative p related to aging, perhaps vascular, or oth lective factor, may contribute to the dev ment of the disease in both stomach and l

Roentgenology

Any intrathoracic or intraabdominal di which may interfere with diaphragmatic m and cause shallow breathing may permit plug of bronchi with secretion resulting in atelec If the obstruction occurs in small bronchi

bronchioles, plate-like atelectasis may result Under certain conditions, an effusion may also develop In a study of 7,064 hospitalized cases, Marks and Nathan found twenty nine with linear atelectasis, 20 per cent occurring in patients with intrathoracic disease and 80 per cent with intra abdominal disease

Fleischner was among the first to draw attention to the significance of these linear striations This investigator suspected that the densities represented areas of atelectasis rather than pleural thickening, a belief held hitherto The affected areas are projected as linear striations in the chest x ray because of the relative fixation of the mediastinum medially and the negative intrapleural pressure peripherally, thereby favoring vertical collapse of the involved portion of the lung The disk like or plate like atelectatic areas appear in the chest x ray as linear streaks in one or both lower lung fields lying in more than one plane, at times in association with a pleural effusion

The differential diagnosis of linear atelectasis and healed pulmonary infarcts which have shrunken asymmetrically may prove difficult Linear atelectasis may also be duplicated roentgenologically by distended lymphatics incident to mitral stenosis and hypertension of the lesser circulation (*see* Chapter 11) Nor is the condition easily distinguishable from interlobar pleurisies On the whole, the significance of linear striations is more readily appreciated in the light of the clinical history than on the basis of roentgen findings alone

Case 28 Male—Age 51

The patient was admitted to a city hospital with a three month history of thirty pounds weight loss, anorexia cough, expectoration diarrhea and abdominal cramps He confessed to have been a moderately heavy beer drinker for some years A chest x ray revealed fluid in the left pleural cavity and a linear density running across the right lower lung field (Figure 53A) The heart was not enlarged Two chest aspirations yielded serous fluid S G 1 018 to 1 020 with a predominance of lymphocytes The sputum did not reveal acid fast bacilli except for one questionable positive culture

The patient was transferred to Seton Hospital with a presumptive diagnosis of tuberculosis A chest x-ray at this time, approximately two months after the initial examination, revealed fluid in the right pleural cavity and horizontal striations across the left lower lung field (Figure 53B) The liver was enlarged and there was possibly also ascites Liver function tests indicated liver disease (cephalin flocculation ++, persistent reversal of A G ratio) A month later a chest x ray showed absorption of the fluid in the right chest leaving several linear densities, seen best in the right lateral projection The patient improved on a high caloric, high protein and high vitaminic diet

The abdominal conditions listed in Table 5, which may cause pulmonary atelectasis of the type described may also provoke pleural effusion In most instances the pleural effusion is due to direct extension of disease to the diaphragmatic pleura In the presence of an acute subdiaphragmatic disease, one may also encounter a transient, "sympathetic" effusion but usually the fluid is part of the infectious process

TABLE 5

ABDOMINAL DISEASES WHICH MAY BE ASSOCIATED WITH INTRATHORACIC LESIONS

Inflammatory Lesions
- Liver Abscess
- Subdiaphragmatic Abscess
- Acute Cholecystitis
- Subacute Pancreatitis
- Acute Pancreatitis
- Periappendiceal Abscess
- Perforated Peptic Ulcer

Neoplasms
- Ovary
- Gallbladder
- Ileum
- Transverse Colon

Miscellaneous Lesions
- Hepatic Cirrhosis
- Incarcerated Abdominal Hernia
- Benign Gastric Ulcer (Weber and Gregg)

From Marks and Nathan *Radiology*, *52* 363 1949

Of particular interest is the finding of a large collection of fluid in the chest, usually a right-sided hydrothorax, accompanied by ascites in patients with cirrhosis of the liver and intraabdominal neoplasms notably ovarian tumors, to be described shortly Williams reported fifteen cases of cirrhosis of the liver with pleural effusion Six of these had antecedent ascites and eight had



Figure 53 Case 28 Cirrhosis of liver with pleuropulmonary manifestations A (*Left*) Obliteration of left costophrenic angle by fluid linear horizontal striation in right lower lung field B (*Right*) Three months later large collection of fluid in right pleural cavity linear horizontal striation in left lower lung field

coincidental cardiac or pulmonary diseases On the other hand fifty four patients showed ascites for considerable periods without demonstrable pleural effusion Christian reported a case of bloody pleural fluid an unusual complication of cirrhosis of the liver A similar case was studied recently at the Montefiore Hospital

Meigs Syndrome

The association of benign ovarian tumors ascites and hydrothorax has been known for many years but the condition was not generally recognized as a clinical entity until Meigs and Cass in 1937 focused attention on this rather bizarre combination now known as *Meigs syndrome* Heretofore the discovery of a pelvic or abdominal mass with pleurisy and ascites was immediately ascribed to advanced malignancy and the patient left to die of a presumably hopeless disease The rapid reaccumulation of the fluid in the chest and abdomen after repeated aspiration seemed all the more in keeping with a malignancy

The importance of recognizing Meigs syndrome lies in the fact that upon removal of the pelvic tumor the fluid in the chest and abdomen quickly absorbs and the patient makes a complete recovery In the original communication by Meigs and co workers the underlying cause was found to be a fibroma of the ovary The list of tumors has since been enlarged to include pseudomucinous cysts of the ovary theca and granulosa cell tumors fibroadenomas uterine tumors and even malignant pelvic tumors with ascites and hydrothorax but without demonstrable cancer cells in the ascitic or chest fluid On several occasions in which I encountered instances of presumably the last mentioned sooner or later they turned out to be malignant tumors with serosal metastases

It is noteworthy that myxedema may be associated with ascites and hydrothorax or hydropericardium without associated cardiac failure Such an occurrence in a female would have to be differentiated from Meigs syndrome Watson and co workers noted in one patient with myxedema that the ascitic fluid gave a positive reaction for mucin These investigators suggest that such effusions might represent an outpouring of mucinous fluid from serous surfaces analogous

to the accumulation of mucinous fluid in other tissues of patients with myxedema. Ferayorni and Sprague also reported a case in which myxedema was associated with hydrothorax and ascites. There was no evidence of heart failure to account for the serous effusions. The effusions regressed after the administration of dessicated thyroid.

The manner of development of hydrothorax in Meigs' syndrome has provoked considerable speculation. Were the mechanism known, it would probably explain also the occurrence of hydrothorax in patients with cirrhosis of the liver, pseudocysts of the pancreas and the several other conditions associated with hydrothorax listed previously. Undoubtedly, many patients with ascites develop fluid in the chest that is not recognized clinically. There is also reason to suspect the hydrothorax rarely occurs without ascites although the presence of the latter cannot always be detected. Meigs quotes Cullen to the effect that "nearly every case of fibroma of the ovary that I have seen has been accompanied by abdominal fluid." In Meigs' experience this held true for about 75 per cent of fibromas.

The relative infrequency of massive hydrothorax, in the presence of ascites of whatever cause, speaks for an interplay of several factors. The diaphragm is richly supplied with lymphatics and it takes only a few minutes for the transfer of particulate matter from the peritoneum to the subpleural lymph nodes and vessels. The major part of the material is carried by the subpleural lymphatics to the dorsal surface of the sternum and thence to the right lymphatic and thoracic ducts. I. C. Rubin and co-workers, in a series of animal experiments, using human serum as well as saline stained with carmine or India ink injected into the abdomen, found that the transfer of fluid from the abdominal into the pleural cavity is not obstructed from below upward but that resorption from the pleural cavity is apparently delayed. Small corpuscular elements like carmine and India ink are easily transported from the abdominal into the pleural cavities. The preponderance of right sided hydrothoraces is assumed to be favored by the better development of the diaphragmatic lymph channels on the right side, the greater activity of the right leaf of the diaphragm and the fact that the pulmonary lymphatic drainage takes place almost entirely through the right lymphatic ducts. A possible hormonal origin of Meigs' syndrome has also been suggested.

Cowan and co-workers had a unique opportunity to investigate the transport of particulate matter between the pleural and peritoneal cavities in a woman of sixty-one who had an ovarian carcinoma with ascites and hydrothorax. In an attempt to repress the ascitic fluid formation and the tumor growth, the patient was treated with radioactive colloidal gold (Au^{198}). As an incidental finding it was noted that a rapid transport of radioactive gold occurred from the peritoneal cavity to the pleural space. A maximum concentration was obtained within two hours. Radioactive gold was found in the abdominal cavity following right pleural space administration with a maximum concentration in one hour. The per cent of dose delivered to the opposite cavity in each instance spoke against a direct communication, rather, for some form of rapid transdiaphragmatic lymphatic transport.

There is, however, the possibility that in some cases an abnormal communication may be present between the pleural and peritoneal cavities. Williams reported a case in which a pleural effusion was apparently due to rupture of the diaphragm in a patient with longstanding ascites due to Laennec's cirrhosis of the liver. Emerson and Davies point out that the occurrence of a massive hydrothorax complicating ascites due to cirrhosis of the liver is characterized by a sudden onset, the appearance of the hydrothorax often coinciding with considerable diminution in the amount of ascites. In a well documented case, they cite an instance where it was possible to show, both by injection of dye into the peritoneal cavity as well as at autopsy, that a minute hole, less than 1 mm. in diameter, was present in the right hemidiaphragm due to a localized separation of the tendonous fibres, through which the ascitic fluid found its way into the pleural cavity. Were it not for the fact that the opening was stained with dye, it could have been easily overlooked. These investigators refer to two other

cases where a hydrothorax followed a diaphragmatic defect It may be pertinent to mention that in a review of thirty-six reported cases of spontaneous pneumothorax, complicating induced pneumoperitoneum, Shapiro found the pneumothorax to have occurred on the right side, in thirty one The cause was usually the result of rupture of herniated peritoneum through a weakened diaphragm

The possibility of a congenital opening being present in the diaphragm causing Meigs' syndrome also arises If the opening is small the liver may block the passage of fluid Deacon reported the finding of a wide channel in one case through which fluid passed readily from the peritoneal to the pleural cavity giving rise to Meigs syndrome As a final note to a complex subject, it should be noted that in some cases ascites and hydrothorax are found in association with relatively small ovarian tumors and it is suspected that the latter may possess a marked secretory power

Case 29 Female—Age 34

The patient was admitted to the Lebanon Hospital because of continued swelling of the abdomen which she had first noted about five mont ously The patient had also noted lately of breath cough, loss of appetite and wei menses had been irregular and the bleedi profuse Examination revealed a thin wor a distended abdomen The chest revealed sion at the right base, the fluid reaching to of the fourth rib in the axillary line (Figu Aspiration yielded 1200 cc of clear, yello Microscopic examination did not reveal tum

The presumptive diagnosis was multiple fibroids associated either with a papillary nom of the ovary or a fibroma of the ovar

At operation, a massive pseudomucinous the right ovary and a intramural fibroi found The ovarian tumor occupied the part of the abdominal cavity About two free fluid similar to that present in the cyst was free in the abdominal cavity The lef appeared normal Microscopic examinati vealed cysts lined by a single layer of co cells of the mucinous or goblet type The str the cyst wall was composed of rather cellular tissue which was quite vascular There was n logic evidence of malignant tissue Follow moval of the cystic ovary, the pleural effusi ascites quickly disappeared and the patient m uneventful recovery (Figure 54B)

Pulmonary Manifestations of Metastatic Diseases

Introduction

There are many circulatory borne diseases which may affect the lungs The incidence of pulmonary involvement and the patterns assumed by the metastatic lesions depend on the nature of the primary disease and the pathways taken by the pulmonary metastases The physical examination of the chest gives no inkling of the presence or absence of metastatic deposits in the lungs let alone the appearance of the individual foci Before discussing several representative forms of metastatic disease which may affect the lungs, it is in order to describe the avenues by which emboli originating in distant parts of the body may gain access to these organs

Pathways of Pulmonary Metastases

Anatomical Considerations

The pulmonary artery, carrying venous blood, arises from the conus arteriosus in the uppe tion of the right ventricle The artery con upward and backward and then divide right and left branches, the former passin hind the ascending aorta and superior vena the latter, in front of the descending aorta branches of each pulmonary artery, after ing the hilus of each lung, follow closel subdivisions of the bronchial tree, both tures being often encased in the same sh With each subdivision the artery rapidly d ishes in diameter so that by the time the reaches the terminal units of the lung the arte is one fourth or one fifth the size of the alv duct Each blood vessel divides into as m radicles as there are atria leading to alveolar the arterioles finally breaking up into innu able capillary clusters which surround the alv The blood becomes oxygenated as it p through the capillary bed and is returned to

posterior surface of the left auricle by four veins which have no valves

In addition to the pulmonary or lesser circulation, the lungs possess a bronchial blood supply, at systemic pressure, which nourishes the stroma The bronchial arteries arise from the thoracic aorta often from the upper thoracic intercostals, internal mammary and subclavian arteries Two or three arteries accompany each bronchus and its subdivisions forming a rich anastomosing plexus about the bronchi, bronchioles lymphoid tissue and lymph nodes the connective tissue septums and pleura They form the vasa vasorum of the pulmonary artery There is some overlapping in the capillary distribution of the pulmonary and bronchial arteries supplying the alveolar ducts It should be noted that the bronchial arteries in man, supply the pleura and this may serve to explain the unusual vulnerability of the pleural serosa to metastatic deposits Distinct bronchial veins are found only at the hilus of the lung the smaller tributaries arising at the site of bronchial divisions The greater part of the blood of both bronchial and pulmonary arteries is returned by way of the pulmonary veins

Pathological Considerations

The pulmonary arteries are, in health, end arteries and do not anastomose with the bronchial vessels the capillary bed between the two systems maintaining functional rather than anatomic continuity The transitional zone is a favorite site of bacterial lodgement However under abnormal conditions in response to increased demand for oxygen, the bronchial arteries become dilated their ramifications more numerous and the capillaries between the pulmonary and bronchial arteries increase in size

In a series of observations on the bronchial arterial circulation in the normal dog's lung, which is strikingly similar to that in man Ellis and co workers found that the bronchial arteries are necessary for the nutrition of the main stem and lobar bronchi in the region of the hilus Distal to the hilar region the blood supplied by the pulmonary artery can maintain the integrity of the pulmonary tissue and the bronchial walls

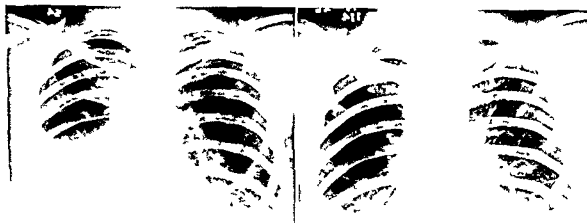


Figure 54 *Case 29* Meigs syndrome A (*Left*) Fluid in right pleural cavity extending along mediastinum and dipping into small fissure B (*Right*) Considerable decrease in size of the pleural effusion (after extirpation of a cystic ovary) (From Rosenfeld *New York State J Med*, 48 527 1948)

It would seem therefore that under normal conditions the bronchial arterial circulation is probably not essential for nutrition of the peripheral parts of the lungs In fact they found that the bronchial circulation may actually be a contributing factor to the development of pulmonary infarction after embolism The hemorrhage that occurs in the pulmonary tissue after pulmonary embolism may come from the bronchial circulation

Ellis and co workers comment that the bronchial arteries may be considered a vestigial circulatory system important to the fetus before birth but of little significance under normal conditions after birth except in the region of the hilus When pathologic processes involve the lungs this vestigial blood supply may again be called upon to fulfill an important nutrient function In support of this belief they cite the anatomical studies of Marchand and co workers who found that the size of the bronchial arteries in the human fetus is nearly the same as that of the adult whereas a great expansion occurs in the pulmonary artery vascular system after birth

The removal of the physiologic screen between the lesser and greater circulations not only increases the blood flow to the tissues thus possibly serving a useful purpose but may also act adversely by allowing the passage of bacteria and carcinomatous emboli between one system and the other also by permitting admixture of venous and arterial blood Studies by Liebow and co workers also Prinzmetal and co workers and others have drawn attention to the many potential channels between the pulmonary artery and vein as well as between the bronchial and pulmonary arteries Liebow and co workers showed that specimens of lung removed surgically from patients with bronchiectasis and prepared for study by the vinylite corrosion technic showed great enlargement of the bronchial arteries and numerous anastomoses of these vessels with the pulmonary arteries The communications were multiple and usually occurred in the walls of the bronchiectatic sacs In half of the specimens the anastomoses equalled or exceeded 1 mm in diameter The anastomoses were so large and numerous as to suggest that they have physiologic importance in shunting pulmonary arterial blood away from diseased tissue into relatively intact parenchyma and as a factor producing hypertension in the pulmonary circulation

In a study of the bronchial pulmonary vascular shunts in patients with pulmonary tuberculosis bronchiectasis and pulmonary cysts Roosenburg and Deenstra demonstrated an increased blood supply from the bronchial arteries via anastomoses to the pulmonary arteries the oxygenated blood from the systemic circulation flowing partially via the normal route to the bronchial veins draining into the pulmonary veins and partially through the pulmonary capillaries Since in the presence of chronic pulmonary diseases little or no gas exchange takes place in the capillaries the large pulmonary veins entering the left heart contain a variable degree of unoxygenated blood a left right shunt The left right shunt may account for as much as one third of the cardiac output and causes an added strain on the heart

Conditions may also arise where the pressure in the pulmonary artery system may be so high as to overcome the normally higher pressure in the bronchial arterial system The venous blood flows through the diseased parts of the lung where it is unable to take up an adequate supply of oxygen The blood is returned to the pulmonary veins in a high degree of oxygen unsaturation The mixed blood may thus reach the heart as a result of a left right shunt having been converted into a right left shunt Until recently the recognition of these arterio venous channels had been of interest primarily to experimental pathologists and physiologists Lately the significance of these shunts has become of increasing importance to physicians and surgeons concerned with precise diagnosis and treatment of diseases of the heart and lungs

PULMONARY EMBOLIZATION

Clinical Features

The incidence of pulmonary involvement of metastatic deposits from distant sites is determined by the avenues of transfer of embolic matter Tumor cells or septic material enter the caval system pass through the right side of the heart the pulmonary arteries and finally lodge

in the capillaries In a series of experiments on the histogenesis of blood borne metastases Baserga and Saffiotti found that tumor emboli spontaneously released by the primary growth are most likely to consist of single or few tumor cells Such tumor emboli lodge in the pulmonary vessels either by adhering to the endothelium of arterioles or by plugging the lumen of capillaries In the arterioles the spread of tumor cells beyond the endothelial wall appears to be preceded by a phase of intraluminal growth The trapped embolus penetrates the vessel wall and eventually develops into a full blown nidus It may be mentioned parenthetically that cancerous emboli may lie dormant in tissues for many years without showing invasive features

More difficult to explain is the absence of pulmonary metastases in the presence of a generalized blood borne disease This is exemplified in the occurrence of limited tuberculous meningitis secondary to urogenital tuberculosis or limited vertebral involvement secondary to cancer of the prostate breast or thyroid Batson is largely responsible for clarifying such apparently paradoxical situations by drawing attention to the fact that a collateral circulation exists between the veins of the chest abdominal wall and vertebral column The vertebral veins lie outside the thoraco abdominal cavity and communicate with the intercostal veins also the veins of the abdomen and with the azygos system of veins Through the latter there is free communication with the posterior bronchial veins and the veins draining the parietal pleura The pressure in this valveless venous system is low so that with every compression of the trunk during strain or cough the pressure is raised sufficiently to shunt the blood flow from the azygos channels into the vertebral system The presence of this paravertebral collateral circulation may serve to explain the high incidence of intracranial metastases of septic bacterial or malignant origin without pulmonary involvement

The manner of spread of malignant cells through the pulmonary lymphatics has aroused considerable interest because of certain clinical and roentgenological features associated with this form of tumor invasion Diffuse carcinomatous involvement of the lymphatics of the lungs and pleura may originate from a small bronchiogenic carcinoma More often the pleuropulmonary implication is secondary to carcinoma of the stomach breast ovary thyroid pancreas or prostate It is still not entirely clear as to whether the lungs are involved by retrograde extension from the hilar lymph nodes along peribronchial and subpleural lymphatics or whether the tumor cells invade initially the lungs by way of the pulmonary arteries gain access to the lymphatics and then spread to the hilar lymph nodes Current opinion veers to the belief that the pleura and lungs are first involved by a hematogenous dissemination of tumor emboli by way of the thoracic duct subclavian veins and the pulmonary arteries After the development of the tumor emboli in the pulmonary capillaries there is lymphatic permeation toward the hilar lymph nodes

Irrespective of whether the neoplasm originates in a bronchus stomach pancreas or other organ the primary growth is apt to be insignificant even microscopic in size Cut section of the involved lung reveals a firm organ with diffuse web like infiltrations along the lymphatics which appear as yellowish white streaks in places showing larger aggregations The involvement is most pronounced in the mid and lower portions of the lungs The lymphatics in the visceral pleura are dilated and streaked with glistening tumor tissue bringing into relief the individual lobules The hilar lymph nodes are as a rule only moderately enlarged This is possibly an additional indication that the original dispersion is peripheral rather than central

It would take us too far afield to dilate on hematogenous tuberculosis pyemia disseminated coccidioidomycosis hematogenous amebic abscesses and other blood borne infections which may involve the lungs and pleura The current use of specific antibacterial measures has reduced greatly the incidence of these once dreaded diseases so that they play a relatively minor role in medical practice In contrast to metastatic pulmonary abscesses one is more apt to encounter bland emboli from phlebothrombosis of the veins of the lower extremities or pelvis These



Figure 55 Forms of metastatic carcinoma of lung A (*Left*) Numerous ovoid densities of uneven size are seen in both lungs especially in the lower lobes (Resection of a carcinoma of the colon five years previously) B (*Right*) Reticular striations permeating both lung fields especially the lower portions circumscribed focus in right upper lobe (Lymphangitic carcinomatosis of the lungs secondary to carcinoma of the thyroid circumscribed focus in right upper lobe was found at autopsy to be a hamartoma)

emboli are more apt to cause pulmonary infarction, the features of which will be described in the following chapter

Theories of Selective Localization of Pulmonary Emboli

There is one aspect to the problem of metastatic pulmonary disease which may be appropriately discussed at this time, namely, why some forms of hematogenous implantations favor the upper lobes and others the lower lobes The theories proposed, and they have been many concern themselves chiefly with explanations for the predilection of reinfection tuberculosis for the apices of the lungs However they have a certain bearing also on the entire problem of pulmonary metastases

Dock postulates that a relative ischemia, due to the relatively lower pulmonary pressure is the cause of apical localization of tuberculosis and for the same reason for the low incidence of progression of the disease in this location Medlar and Sasano evolved an upright theory' by which it is postulated that the entire lung is at first uniformly seeded but that the tubercle bacilli disappear from the lower lobes and progress in the upper lobes as a result of the inadequate blood circulation of the apices in the upright man In a series of experiments in rabbits these investigators found that when the animals were forced to sit upright, the lesions were more numerous in the upper lobes

Smith and co-workers found that the upper lobes are infected with tuberculosis directly and immediately because the stream flow ' of blood through the heart is directed to the upper lobes They conclude that the apical lesions in tuberculosis do not depend upon an inadequate circulation rather on the position of the animal which determines the path taken by the stream flow of blood through the heart In other words they confirm the observations of Medlar and Sasano but not the interpretation Using animals as well as synthetic plastics Smith and co-

workers studied the problem not only with respect to tuberculosis but also with respect to pulmonary emboli and infarcts which favor the lower lobes According to their "stream flow" theory it is postulated that in the case of tuberculosis pus or small caseous particles discharged from infected lymph nodes and carried by way of the thoracic duct and left subclavian vein to the right auricle right ventricle and into the pulmonary artery are deposited in the upper lobes because there is little mixing of the blood in the upper stream with that entering the same chambers by way of the inferior vena cava Each column of blood is presumed to pass in a layer through the right side of the heart into the upper and lower parts of the lung respectively

The "stream flow" theory according to these investigators explains the apical localization of tuberculosis, also the basal preference of emboli and infarcts arising in foci of phlebothrombosis in veins of the lower extremities and abdomen According to this theory blood borne metastases to the lungs follow the simple hydrodynamic principle that fluid of the same viscosity may flow side by side through tubes for considerable distance with a minimum of admixture The "stream flow" theory is the seventeenth one proposed to explain why different metastatic diseases of the lungs favor particular parts of the organs There will probably be additional theories

Roentgenology of Metastatic Pulmonary Lesions

As indicated the site of the primary tumor



Figure 56 Alveolar cell carcinoma of lung (Pulmonary adenomatosis) simulating metastatic neoplasm A (*Left*) Ill defined single and confluent densities scattered in both lungs (Clinical course characterized by loss of weight increasing dyspnea and profuse mucoid expectoration Smears from bronchoscopic washings and from sputum showed cells suggestive of alveolar origin Total duration of the disease from onset of striking symptoms to death fifteen months) B (*Right*) Microscopic section of lung shows mucus secreting tumor lining alveolar septa alveoli filled with mucus with nests and cords of exfoliated tumor cells (Gross appearance of lung resembled a pneumonia in a gray stage of hepatization)



Figure 57 Solitary metastasis of lung A (*Left*) Large, ovoid density in left midlung B (*Right*) After resection of left lower lobe (Specimen revealed malignant melanoma primary growth appeared in right shoulder six years previously, treated with radiotherapy and later with radical excision metastases appeared in pelvis several months after operation)

and possibly the avenues by which the lungs are invaded, determine the nature of the metastatic lesions Tumors of the breast and stomach are apt to spread to the lungs and pleura by way of the lymphatics either through the thoracic or right lymphatic ducts Tumors in organs closely associated with the systemic venous circulation, such as renal and skeletal malignancies, show a particularly high incidence of pulmonary metastases Although pelvic tumors may spare the lungs careful postmortem studies show frequent pulmonary involvement In a correlative study of the postmortem and roentgen findings of a large number of patients treated at the Montefiore Hospital, Fried found pleural or pulmonary involvement in 54 per cent of renal neoplasms in 43 per cent of cancer of the prostate but in only 7 per cent of cancer of the bladder Willis found pulmonary metastases in 30 per cent of all fatal cases, being present in 75 per cent each of instances of chorionepithelioma osteosarcoma and renal carcinoma, 65 per cent of carcinoma of the thyroid, 60 per cent of melanoma, 55 per cent of carcinoma of the breast 40 per cent of carcinoma of the esophago gastrointestinal tract, 30 per cent of oral and pharyngeal carcinoma, 20 per cent each of hepatic and pancreatic malignancies, 15 per cent of uterine malignancy and 10 per cent of ovarian carcinoma

With occasional exceptions, metastatic tumors spreading through blood channels involve both lungs with nodular densities varying in size from miliary to large masses Occasionally the chest x ray reveals a solitary, circumscribed lesion and unless one is aware of the nature of the primary disease, the differential diagnosis between a primary and metastatic lesion may be quite difficult Lymphangitic carcinomatosis permeating the lungs and pleura is characterized by a diffuse reticulation interspersed with nodulations affecting symmetrically both organs If the primary focus is in the lung, the lymphatic spread may be regional

Although a number of attempts have been made to classify the roentgenologic appearances of metastatic pulmonary neoplasms into various

patterns such as miliary, nodular (Figure 55A), infiltrative, lymphangitic (Figure 55B), massive and cavitating forms, clear-cut differentiations are not feasible and of minor clinical significance Primary carcinoma of the lungs may simulate metastatic disease (Figures 56A and B) Of more practical importance is the fact that a solitary metastasis in a lung may be amenable to resection and the life of the patient prolonged Unfortunately, resectable pulmonary tumors are met in a very small percentage of patients with metastatic cancer (Figures 57A and B) In an analysis of 314 cases of metastatic pulmonary neoplasms observed in a five-year period, Minor found two cases in which resection was actually carried out These two patients were still alive and free of malignant disease more than four and seven years after their pulmonary resections It is noteworthy that the first record of a successful resection for metastatic cancer of the lung was reported by Barney and Churchill in 1939 The particular patient had had a nephrectomy for a hypernephroma fifteen months previously and was alive and well twelve years after the lobectomy

In 1950, Seiler and co workers found reports of sixty eight cases treated by resection for metastatic pulmonary lesions The tumors most frequently resectable are those secondary to carcinoma of the large bowel (eleven cases) hypernephroma (seven cases) fibrosarcoma (seven cases) and carcinoma of the ovary (five cases) With several exceptions, the patients with long intervals of time elapsing between the occurrence of the primary and the secondary tumors did no better than the group as a whole Bronchial involvement was noted in 63 per cent of the cases in which the reports especially mentioned this feature or in 27 per cent of the entire group Higginson found bronchial involvement in nine of thirty five cases In eight of these (22 8 per cent) bronchoscopic biopsy was positive Of the thirty five pulmonary metastatic malignancies, twenty six came to surgical exploration and of these, twenty-two were resected In two patients, two or more resections were done for re-



Figure 58 *Case 30* Solitary metastasis to lung three years after resection of a portion of colon for adenocarcinoma A (*Left*) Circumscribed density in right middle lobe B (*Right*) After excision of right middle lobe (Microscopic examination of tumor revealed adenocarcinoma identical in appearance with that resected from the colon)



Figure 59 Metastatic carcinoma of bronchus primary in the colon A (*Left*) Triangular density at base of right upper lobe adjacent to the hilum, above horizontal fissure which is accentuated and slightly displaced up ward (Expectorated piece of tissue revealed histologically adenocarcinoma Bronchoscopy showed an obstruction of the right upper lobe bronchus Biopsy specimen also revealed adenocarcinoma) B (*Right*) Two months later considerable diminution in size of the density (*Patient died six months later of generalized carcinoma*) (*See* Figure 87)

current metastases Metastatic pulmonary malignancies secondary to carcinoma of the large bowel offered the best prospects of resectability

Case 30 Female—Age 59

Three years previously the patient had a resection of a portion of the colon for adenocarcinoma She felt well until late in 1954 when she developed pain in the right lower chest, moderate cough, expectoration slight dyspnea on exertion and wheezing The physical examination was noninformative The chest x-ray showed a well circumscribed density in the region of the right middle lobe (Figure 58A) In view of the past history of carcinoma of the bowel it was suspected that the lesion in the lung represented a metastatic deposit although a primary carcinoma of the lung could not be excluded The patient was admitted to the Montefiore Hospital A bronchoscopy was negative A search for possible metastases elsewhere in the body was unrevealing

On December 17, 1954 the patient was operated on by Dr Morris Rubin The pleural cavity contained no free fluid and there were no visible metastases Palpation of the mediastinum and hilum revealed no abnormalities The upper and lower lobes appeared normal The right middle lobe was completely shrunken and contained a mass about the size of a large walnut Further inspection revealed no other masses or enlarged lymph nodes In view of these findings, the right middle lobe was resected The specimen revealed a well circumscribed mass of grossly recognizable tumor It was pale, yellowish gray with foci of necrosis The bronchi leading to the tumor were not invaded The surrounding tissue appeared grossly unremarkable The microscopic examination showed the tumor to be composed of well developed adenocarcinoma The bronchi showed no evidence of malignant changes The tumor itself appeared compatible with metastatic carcinoma originating in the bowel A review of the microscopic sections of the previously resected colon showed identical histological features

After operation the upper and lower lobes reexpanded completely and the patient was discharged two weeks later in good condition (Figure 58B) She has remained well without signs of recurrence of the disease, when examined one year later

Rare instances are on record of malignant tumors metastasizing to the trachea or bronchi which may simulate primary tumors Cohen re-

ported an instance of a solitary pulmonary metastasis with detectable bronchial involvement which appeared nine and a half years after resection of a colon carcinoma The author found reports of thirteen additional cases in which bronchial invasion by a pulmonary metastasis was demonstrated endoscopically I have had a similar experience The patient a physician aged sixty one had had a resection of the sigmoid colon four years previously The present illness began with cough and expectoration On one occasion the patient spat up a small piece of tissue which on histologic examination revealed adenocarcinoma similar to that obtained from the resected colon At this time also the chest x ray showed a density at the base of the right upper lobe near the hilum immediately above the horizontal fissure which was accentuated and displaced upward (Figures 59A and B) Auscultatory findings were in keeping with bronchial obstruction the latter being confirmed on bronchoscopy, the biopsy specimen also revealed metastatic carcinoma The patient died six months later

It is well to bear in mind that although lesions found in the lungs of patients who have had previous resections may be assumed to be metastatic, occasionally one may be dealing with a second primary in the lung With the marked increase in bronchiogenic carcinoma this possibility is more than of academic importance Poppe encountered four patients with primary carcinoma of the lung who had had previous resections of the large bowel for primary malignancies Three of these had been allowed to reach an inoperable stage, on the assumption that the lung tumor was metastatic from the rectum Poppe concludes that a more optimistic attitude about resecting metastatic pulmonary malignancies may save a few patients with primary carcinoma of the lung

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Chapter 11

Pulmonary Manifestations of Cardiovascular Diseases

Introduction

THE BLOOD FLOW through the heart and lungs is so finely adjusted that any interference with the circuit is quickly felt in both organs For the moment we are concerned with disturbances in the cardiovascular apparatus which may be reflected in the lungs to a significant degree Certain features relating to the blood supply of the lungs were discussed in the preceding chapter in relation to metastatic pulmonary disease The following will deal more specifically with cardiovascular pulmonary derangements One cannot separate cardiopulmonary functional disturbances and intrinsic disease of blood vessels or the latter and resulting parenchymal lesions The order in which the several morbid states will be considered is therefore not intended to serve as a nosological classification of cardiopulmonary disease The description will be limited to basic mechanisms and the more prominent clinical features of the several conditions mentioned, with special reference to the chest x ray findings

Cardiopulmonary Dynamics

The right side of the heart, the depot of the *pulmonary circulation*, accommodates the same amount of blood in a given unit of time as that discharged by the left side of the heart into the aorta and systemic circulation The blood capacity of both lungs potentially equals that of the remainder of the body Congestive heart failure is a sign that the right side of the heart is unable to accept and expel the venous blood brought to the right auricle and right ventricle In time this gives rise to peripheral blood stasis and edema The cause of the right ventricular failure may be a preexisting insufficiency of the left ventricle or disease of the pulmonary valves or disease of the lungs or blood vessels causing pulmonary hypertension and right heart strain

The lungs ordinarily hold about 9 per cent of the total blood volume during inspiration and about 6 per cent during expiration The systolic pulmonary pressure is only one-sixth that of the systemic (i e , 20 mm of mercury) It is obvious, therefore, that under stress the lungs are able to accommodate many more times their normal load Thus, when congestion occurs, a large volume of blood is able to accumulate in the lungs In health there is a wide safety zone before the critical period is reached Massive intravenous infusions may be introduced in the experimental animal without causing pulmonary edema unless the pulmonary venous pressure is increased by artificial means The great adaptability of the lungs to increased demand is also evident from the following After exercise the cardiac output may rise four-fold, from 5 liters per minute to about 20 liters per minute, whereas the pulmonary ventilation may increase more than fifteen-fold, from a resting minute volume of 8 liters to as much as 125 liters (Drinker)

The pressure and volume *differences* between the lesser and greater circulations are reflected in the relative muscular thickness of the two ventricles, the wall of the left ventricle being normally about twice as thick as that of *the right* Other *points of difference* also exist between the pulmonary and systemic circulations, there being no interdependency between the one and

the other The arterial pressure may be normal or even below normal in one and high in the other The autonomy of functions between the greater and the lesser circulations may be determined by instrumental means as well as by the behavior of the circulation in the two systems in response to drugs Intravenous administration of aminophyl line causes an abrupt decrease in the arterial pressure of the greater circulation but does not have a hypotensive effect on the smaller circula tion Other drugs affect the two circulations in opposite manner The lesser circulation has its own neuroregulatory system which is independ ent of that of the greater circulation

In essence the right side of the heart stands in the same relation to the lesser circulation as the left side does to the greater circulation the min ute output of blood from the right ventricle equaling that ejected by the left ventricle Inspi ration not only fills the alveoli with air but also aids in filling the capillaries with blood Expira tion helps to expel blood as well as air from the lungs Disturbances in the mechanics of the lesser circulation react on respiration just as disturb ances of respiration react on the lesser circulation Likewise the symptoms of pulmonary and car diac insufficiency, both primarily expressed in anoxia resemble each other so closely that one is often hard pressed to distinguish the one from the other In advanced cardiopulmonary failure it may be a matter of academic interest whether the insufficiency is mainly cardiac or pulmonary usually it is a combination of both But before this stage is reached it is important to differen tiate the two components in order to treat the im pending breakdown intelligently Recent studies with cardiac catheterization and cardiopulmo nary function tests have served to shed consider able light on the subject especially on the role played by pulmonary hypertension

Pulmonary Hypertension

Physiological Considerations

Many factors are at play in regulating the blood flow in the lesser circulation The short wide pulmonary artery with its rapid subdivisions and immense capillary network placed between countless alveoli offers an ideal arrangement for complete oxygenation and speedy return of the blood by way of the four veins to the left auri cle It is noteworthy that the pulmonary arteri oles have six to eight times the diameter of the arterioles of the greater circulation The lung capillaries are also very wide In heart failure associated with hypertension of the lesser circu lation the lung capillaries may dilate ten to thirty times their normal size (Weiss)

Hypertension of the lesser circulation may arise under varied circumstances In recent years a primary form of hypertension has been recog nized associated with right ventricular hyper trophy and usually with variable degrees of pulmonary vascular sclerosis No demonstrable cause is found in this type of so called essential or primary hypertension there being no recog nizable antecedent cardiac or pulmonary disease Eventually symptoms and signs of right heart failure appear The important role played by vascular shunts in causing obstruction and hyper tension of the lesser circulation was mentioned previously Brinton believes that primary pul monary hypertension results from excessive entry of blood into the lesser circulation from the bronchial arteries The blood injected under systemic pressure causes dilatation and sclerotic changes in the pulmonary artery and hyper trophy and eventual failure of the right ventricle

In the vast majority of instances of pulmonary hypertension the increased pressure in the lesser circulation is secondary to some other disturbance including (1) obstruction of the lesser circula tion beyond the pulmonary system as exempli fied in mitral stenosis and a failing left ventricle of whatever cause and (2) obstruction within the pulmonary system either in the main pulmo-nary artery by an embolus or as a result of throm bosis of branches of the pulmonary artery by vascular fibrosis The last mentioned is encount ered in association with lymphangitic carcinoma tosis schistomiasis primary pulmonary arteriolo sclerosis polyarteritis nodosa and other diseases associated with widespread interstitial fibrosis and

capillary vascular involvement. In addition, secondary pulmonary hypertension may be due to alterations in the thoracic cage as a result of thoracoplasty or kyphoscoliosis.

Roentgenology

Signs of pulmonary hypertension are recognized in the chest x-ray as a result of the secondary effects of the increased pressure in the heart and in the pulmonary blood vessels. In severe mitral stenosis associated with pulmonary hypertension, the left hilum is frequently concealed by a dilated main pulmonary artery and its left branch. The right hilum is usually accentuated. The lung parenchyma shows loss of normal translucency due to a profusion of blood vessels. But it is difficult to reconcile the roentgen appearances of the latter in all cases with the angiographic observations of Goodwin and coworkers who found that in patients with pulmonary hypertension the main arteries are enlarged but the distal branches are narrowed, irregular and tortuous, especially in the lower lobes. These investigators found that the severity and extent of the vascular changes bore a close relation to the degree of pulmonary hypertension.

Attention has been recently drawn to the presence of small horizontal lines at the bases of the lungs as an indication of pulmonary hypertension in the presence of mitral stenosis (Figures 60A and B). These lines are sharp, well defined and are arranged in parallel fashion, one above the other near the costophrenic angles. The lines lie immediately beneath the pleura. Kerley found these lines in silicosis, pneumonoconiosis and other diseases. Davies and coworkers noted these lines, referred to as "Lines B of Kerley," in pulmonary hypertension. According to Kerley, also Carmichael and coworkers, these lines are presumed to represent overloaded intercommunicating lymphatics due to disturbed flow of the lymphatic circulation. It might be mentioned at



Figure 60. Advanced rheumatic heart disease with mitral stenosis and pulmonary hypertension showing "Lines B" of Kerley. A (*Left*). Markedly enlarged heart with prominent pulmonary conus. Fluid in left chest, increased vascular markings. Linear striations arranged in parallel fashion are seen at the base of the right lower lobe. B (*Right*). Detail of right lower lobe. (Transbronchoscopic atrial pressure determinations revealed a mean pressure of 25 mm. Hg.)

this point that according to Dock the flow of lymph increases with the rise of venous pressure and is most rapid and effective at the lung bases

Short found that these striations or as he prefers to term them septal lines correspond both in size and distribution with the interlobular septa although Kerley believes the lines are too long to be interlobular septa Short suspects that the lines represent ingrowths from the subserous areolar tissue that invests the lung The interlobular septa are traversed by tributaries of the pulmonary venous system and also by the lymphatic channels that link the deep lymphatic system with the subpleural network The prominence of the interlobular septa, according to Short must therefore be due to enlargement of one or more of these structures At first the enlargement of the septa is due to edematous swelling of areolar tissue later from fibrosis This may explain why in some cases septal shadows persist unchanged after relief of the stenosis In the usual chest x ray taken for cardiac disease the overexposed film is apt to miss the delicate striations

Short studied the radiographic appearances of the lungs in thirty three patients with rheumatic mitral stenosis in whom at operation or necropsy the maximum diameter of the mitral valve was 1 cm or less The lung architecture was abnormal in varying degrees in each patient Septal lines were found in twenty five cases and although never the sole abnormality they were sometimes the most impressive Serial chest x rays showed the changes to be persistent and slowly progressive In Short s opinion *a normal lung architecture is inconsistent with a diagnosis of severe mitral stenosis*

Confirmatory observations of the significance of these lines as an indication of pulmonary hypertension *in patients with mitral stenosis* have been reported by Levin This investigator reviewed the chest x rays of sixty three patients with a clinical diagnosis of *mitral stenosis* Each was studied by right heart catheterization pulmonary artery pressure and twenty seven of these also by pulmonary wedge pressure Thirty nine (39) patients showed typical septal lines A positive correlation was found between the degree of basal striae and pulmonary artery and wedge pressures the higher the pressure the more frequent the basal striae Current opinion favors the view that septal lines encountered in patients with hypertension of the lesser circulation are due to edema and associated distention of the lymphatics in the interlobular septa Grainger and Hearn found the lines in predominant mitral regurgitation as well as in mitral stenosis They did note however that patients with predominant mitral stenosis showing septal lines on their preoperative chest x ray almost invariably improved after a technically successful valve operation

I have noted basal striations of the type described in patients in whom there was no reason to suspect pulmonary hypertension (*see* Figures 14 and 15) Grainger and Hearn state that septal lines are seen in any condition in which there is *impairment of pulmonary lymphatic drainage* These include lymphangitic carcinomatosis Hodgkin s disease leukemia pneumonoconiosis *after ligation of the thoracic duct* and with any form of reticulosis affecting the mediastinal lymph nodes

Pulmonary Arteriosclerosis

Sclerosis of the pulmonary artery and its larger subdivisions is quite frequent the condition increasing in incidence and degree with age The process may be part of a generalized atherosclerosis affecting the entire vascular system or it may be present to a greater degree or even be limited to the pulmonary blood vessels The pathologic changes consist initially in an increase of elastic tissue in the media of the smaller branches of the pulmonary artery Soon there is intimal thickening and later fibrous tissue reaction and obliteration of the vessel lumen by organized thrombi and intimal proliferation Recanalization is often seen

The diseases leading to hypertension in the lesser circulation also cause *pulmonary arteriosclerosis* These include mitral stenosis intra auricular septal defects chronic pulmonary infections and the *several conditions mentioned in* the preceding section Diffuse vascular sclerosis

of the medium and smaller sized branches so called hyperplastic arteriolar sclerosis may be associated with hypertension of the lesser circulation syphilis rheumatic fever or it may be present without any apparent cause In the case of the last mentioned there is an increasing body of opinion to support the belief that the unexplained sclerosis is related to an essential form of hypertension of the lesser circulation

Primary pulmonary sclerosis without antecedent lung or heart disease has attracted particular attention because the condition may give rise to a characteristic clinical syndrome so called Ayerza s disease This disease occurs most often in the syphilitic although syphilis is not the sole cause The patient with Ayerza s disease is cyanotic as a result of the accompanying anoxemia but has comparatively little dyspnea Sooner or later edema sets in as well as other evidence of right heart failure The condition has been described in detail by Brenner and more recently reviewed by Leopold Brill and Krygier analyzed twenty instances including one of their own The signs and symptoms do not differ significantly from those occurring in other types of chronic cor pulmonale

The chest x ray findings in pulmonary arteriosclerosis are referable chiefly to the hypertension of the lesser circulation which usually coexists There is accentuation of the pulmonary conus and prominence of the hilar vascular markings In rare instances one can discern distinct sclerotic changes in the vessel walls The secondary polycythemia usually accompanying the condition does not produce demonstrable changes in the chest x rays unless there is pulmonary infarction Since it may be difficult at times to differentiate polycythemia vera from secondary polycythemia Hirsch also Hodes and Griffith have drawn attention to the fact that in the former one may encounter discrete spherical lesions involving especially the middle zones of the lungs whereas in the secondary form there is more apt to be hyperillumination of both lung fields and an accentuation of the hilar vascular markings Chapter 5 which deals with the pulmonary manifestations of blood disorders contains additional comment on the subject

Pulmonary Congestion and Edema

Physiological Considerations

In the presence of left ventricular failure if the cardiac venous inflow and right ventricular function remain adequate pulmonary congestion occurs which sooner or later leads to edema The high capillary pressure stasis and anoxia are important elements in the transudation of fluid in the lung In slow blood flow the active factors are also chemical in nature Once the activity of the several factors reaches a certain critical point edema can progress with great rapidity often with fatal results Hayward found that pulmonary edema does not occur unless the left atrial and pulmonary capillary pressures exceed the effective plasma osmotic pressure by a considerable margin In addition to high capillary pressure possibly a neurogenic factor may suddenly increase the capillary permeability A vicious cycle is established between the low intrathoracic pressure which serves to increase the pulmonary congestion and the hyperventilation caused by dyspnea which further lowers the intrathoracic pressure (Drinker)

The transudation of fluid through the damaged capillary walls into the alveoli and the whipping up of this fluid into froth by respiratory activity cause increasing obstruction of the small air passages impede gas exchange and results in asphyxia The dyspnea cyanosis and bubbling rales of acute pulmonary edema are readily explained on the basis of this mechanism In the initial stages the condition is reversible In chronic heart failure changes take place in the alveoli which become thickened and rigid by the deposition of collagen According to Hayward the fact that acute pulmonary edema does not necessarily occur in spite of high pulmonary capillary pressure suggests either that the fluid is hindered in its escape into the interstitial tissue of the lung and air passages by the structural changes in the capillary walls and alveolar epithelium or that it is rapidly removed by the pulmonary lymphatic system

Clinical Features

The causes of pulmonary congestion and edema are many and varied The major ones are left ventricular failure secondary to hypertension of the greater circulation also coronary artery disease with myocardial infarction and valvular disease of the heart In an analysis of 500 autopsies Cameron found that hypertensive heart disease, excluding chronic nephritis showed an incidence of pulmonary edema in 86 per cent, chronic nephritis 74 per cent, complete coronary obstruction 68 per cent, mitral stenosis, 65 per cent, and almost equally high percentages associated with cerebral hemorrhage, fractured skull, multiple fractures without cerebral hemorrhage, and pulmonary embolism Additional causes are irritating gases neurogenic disturbances, excessive or rapid parenteral administration of fluid as well as rapid paracentesis (Figures 61A and B)

A comprehensive discussion of the clinical features of pulmonary congestion and edema is beyond the scope of this book Suffice it to mention that the initial manifestations of left ventricular failure are usually referable to the lungs The passive congestion and recurring episodes of acute pulmonary edema lead to various gradations of dyspnea ranging from mild shortness of breath after exertion to Cheyne Stokes respiration In time, persistent cough expectoration and occasionally pain in the chest are caused by the resulting chronic pneumonitis and intercurrent infarctions, the congested lungs favoring the occurrence of the latter In addition there are symptoms and signs referable to the failing heart itself

With increasing cardiac decompensation exertional dyspnea comes on with the slightest effort so that soon the shortness of breath is present even when the individual is at rest The dyspnea associated with a failing left ventricle characteristically occurs in paroxysms especially when the individual is recumbent, at which time the engorgement of the pulmonary circulation is greater The individual is aroused during sleep by a seizure of cough, wheezing respiration and considerable distress, a condition commonly referred to as "cardiac asthma" Severe seizures are associated with cyanosis, tachypnea, audible rales expiratory dyspnea and expectoration of frothy, pink stained sputum indicative of pulmonary edema Unless one is aware of the patient's cardiac status and previous state of health, cardiac asthma may be mistaken for bronchial asthma and treated injudiciously with epinephrine and other bronchodilators instead of morphine and its analogues which are effective drugs for the condition

Roentgenology

Until recently the preclinical phenomena associated with pulmonary congestion and edema occupied the attention chiefly of physiologists and pathologists The physician saw only the late stages of the disease With greater use of roentgenography, the problem is assuming increasing clinical interest Inasmuch as pulmonary congestion in its initial stages is transient and symptomless and, in advanced stages, the patient is apt to be too ill to stand a painstaking examination the use of roentgenography, particularly in routine hospital admissions has been of inestimable value in enlarging the understanding of this condition

The roentgen features of pulmonary engorgement and edema are related to disturbances in cardiopulmonary dynamics, mentioned earlier in the chapter Simple engorgement of pulmonary blood vessels without significant transudate in the alveoli is revealed in an accentuation of the hilar vascular shadows and of the adjacent lung markings The appearance of the congested lungs varies depending on whether the condition is acute or chronic and on the presence or absence of associated lung and pleural changes

Figure 61 Acute pulmonary congestion and edema after rapid intravenous instillation of 2500 cc of 5 per cent glucose in saline A (*Upper*) Diffuse ground glass cloudiness of both lungs chiefly the right. (Patient admitted with abdominal pain chill and fever Operated on for an acute pelvic abscess Continued high temperature and shortness of breath at the time chest x ray was taken) B (*Lower*) One week later almost complete resolution of the opacity





(See legend on opposite page.)

In acute left ventricular failure, pulmonary edema manifests itself in a diffuse "butterfly" or "bat's wing" cloudiness of the central portions of the lungs, the opacity extending laterally from the hilar regions (Figures 62A and B) The "butterfly" appearance takes its descriptive from the, more-or-less, symmetrical, perihilar, confluent densities with irregular margins which characterize the lesions and the surrounding offset of translucent apical, basal and lateral zones The "butterfly" shadows, encountered in acute pulmonary edema, do not depend on any specific changes in the tissues, rather on the fact that the lesions are concentrated in the medulla or interior portions of the lungs, as suggested by Herrnheiser and Hinson

Gould and Torrance devised the following classification of pulmonary edema from the viewpoint of the roentgenologic-morphologic features (Table 6)

TABLE 6

Morphologic Classification of Pulmonary Edema

Type I	Central edema Large confluent or even homogeneous dense, central or perihilar opaque shadows usually *forming* symmetrically bilateral densities giving the so called butterfly or bat's wing appearance
Type II	Diffuse edema Patchy, ill defined usually *bilateral densities variable in size* and distributed in a diffuse fashion These shadows are frequently of varying density
Type III	Focal edema (a) Lobar dense, homogeneous consolidation bounded by a major fissure or fissures predominantly lobar in distribution (b) Pseudosarcoma one or more isolated large rounded discrete shadows resembling primary or metastatic tumor

From Gould and Torrance *Am J Roentgenol*, 73 366 1955

Azotemia with Pulmonary Manifestations

Etiologic Considerations

Because of unusual interest expressed on the subject, the pulmonary lesions occasionally found in the presence of azotemia will receive special consideration Basically, however, the mechanism is the same as that underlying acute pulmonary edema As in the latter, the primary cause of the pulmonary lesions in azotemia is left ventricular failure and fluid retention The degree of elevation of the nitrogenous products *in the blood does not parallel the lung changes* and in extrarenal azotemia, without hypertension *lung changes are not observed Furthermore,* experimental ligation of the ureters in animals *thereby inducing death of uremia, is usually not* associated with abnormal roentgen changes in *the lungs unless the animals are also subjected to* fluid infusion (Olsson)

There are some grounds for the belief that in cardiorenal disease associated with azotemia, an *increase in capillary permeability*, due to excess nitrogenous products in the blood, may be a con*tributing element in the lung changes.* Hopps and Wissler found that the lesions of "uremic pneumonitis" *may occur with little or no clinical* or pathologic evidence of left heart failure In their experience, the development of pulmonary lesions was more readily correlated with the degree of acidosis, as judged by the depression in blood CO_2 combining power

Hayward recognizes a subacute form of pulmonary edema occurring in uremia, malignant hypertension, acute nephritis, in occasional cases of polyarteritis nodosa and in association with the rheumatic" lung in acute rheumatism The condition is characterized by clotting and organization of the interstitial and alveolar exudate and is probably caused by a combination of left ventricular failure and altered capillary permeability The pathological, clinical and roentgenological changes are identical in the several conditions mentioned The scarcity of adventitious sounds in the lungs is explained by the organization of alveolar exudate which has a high fibrin content

The so called 'azotemic lung" is a heavy, firm voluminous organ, partly or wholly covered by a fibrinous pleurisy Microscopic examination reveals an irregular distribution of intra alveolar fibrinous or albuminous exudate, thickening of alveolar septa and a mononuclear cell reaction

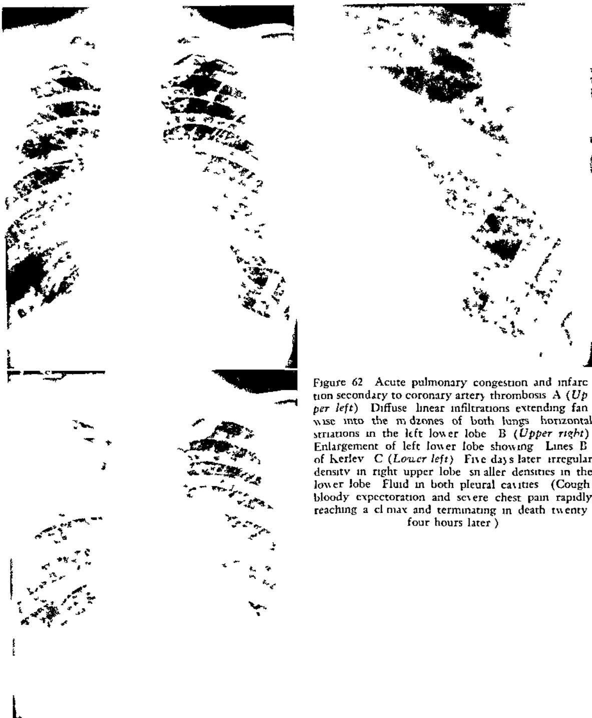


Figure 62 Acute pulmonary congestion and infarction secondary to coronary artery thrombosis A (*Upper left*) Diffuse linear infiltrations extending fanwise into the midzones of both lungs horizontal striations in the left lower lobe B (*Upper right*) Enlargement of left lower lobe showing Lines B of Kerley C (*Lower left*) Five days later irregular density in right upper lobe smaller densities in the lower lobe Fluid in both pleural cavities (Cough bloody expectoration and severe chest pain rapidly reaching a climax and terminating in death twenty four hours later)



Figure 63 Azotemia with pulmonary lesions A (*Left*) Enlarged heart B (*Right*) Nine months later ill defined irregular densities extending fanwise into mid and upper lung fields pleural reaction at bases (Hypertensive cardiorenal disease, admitted in severe uremia autopsy showed marked pulmonary edema hemorrhage and possibly uremic infarcts hypertensive heart disease contracted kidneys) (From Rubin *Diseases of the Chest* W B Saunders Co)

The capillaries are engorged with red cells The alveolar ducts are often prominent showing a pseudomembrane which also lines the alveoli Depending also on associated cardiac disease there are patches of hemorrhage throughout the organ and often areas of infarction In addition one finds evidence of renal disease

Roentgenology

The chest x ray reveals uneven mottling extending from the hilar regions into the adjacent portions of the lung obscuring the normal root shadows The distribution is fanwise the periphery apices and bases of the lungs being spared (Figure 63) The conglomeration of irregular densities in the midzonal portions of the lungs surrounded by a fairly well illuminated zone of tissue may be quite striking especially in the absence of significant symptoms or signs referable to the chest There are times when the x ray appearance alone may be sufficiently impressive to suggest the possible existence of azotemia and prompt the physician to investigate further for its presence But as mentioned the same roentgen configurations may be obtained in pulmonary edema caused by acute left ventricular failure without renal insufficiency In some cases the changes are not widespread and may even be limited to one lung Of 100 cases of pulmonary edema Gould and Torrance found ninety with central edema seven with diffuse edema and three with focal edema Of the group with central edema thirteen could be classified as pure uremic i e those due to primary renal disease and ten as uncomplicated uremic i e renal failure secondary to other disease usually advanced essential hypertension

It is noteworthy that anaphylactic reactions occurring during drug sensitization or after blood transfusions with incompatible blood and associated with acute glomerulonephritis and pulmonary edema may produce roentgen changes in

the lungs or a type described above (Figure 64) In a study of the roentgenological and pathological findings in antigenic (azotemic) pneumonitis Sante and Wyatt cite the work of Trueta Prichard and their co workers with respect to the ischemia of the kidney after injection of bacterial toxin into the renal circulation thereby producing anuria Sante and Wyatt speculate that a similar mechanism might be at play under the influence of the same toxic agent and that the so called azotemic lung might also be due to ischemia of the parenchymal circulation of the lung They suggest the more appropriate term antigenic pulmonary edema

Three years later Prichard and co workers reported additional observations which would

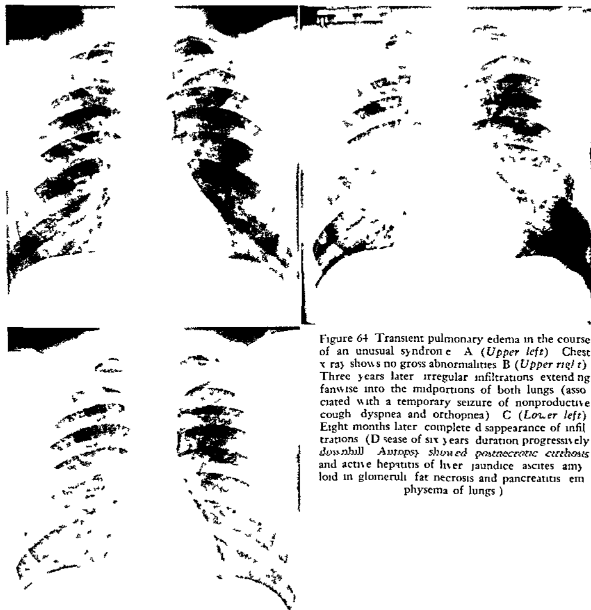


Figure 64 Transient pulmonary edema in the course of an unusual syndrome A (*Upper left*) Chest x ray shows no gross abnormalities B (*Upper right*) Three years later irregular infiltrations extending fanwise into the midportions of both lungs (associated with a temporary seizure of nonproductive cough dyspnea and orthopnea) C (*Lower left*) Eight months later complete disappearance of infiltrations (Disease of six years duration progressively downhill *Autopsy showed postnecrotic cirrhosis* and active hepatitis of liver jaundice ascites amyloid in glomeruli fat necrosis and pancreatitis emphysema of lungs)

seem to bear out the aforementioned speculations In a series of angiographic experiments in animals these investigators were impressed with the frequency with which peripheral ischemia occurred in the midportions of the lungs The chest x ray presented bat s wing shadows as noted in subacute pulmonary edema complicating left ventricular failure These investigators suspect that the condition in man may be associated with a change in the distribution of the pulmonary blood flow such as that seen in their experimental animals They found that blood can pass from the pulmonary arteries to the pulmonary veins into the deeper parts of the lung without circulating through the peripheral portion This may give rise to the roentgen bat s wing shadows Reference is also made to the angiocardiographic studies of Goodwin and co workers who found that in patients with severe mitral stenosis and pulmonary hypertension there were indications of an occlusive process or spasm occurring in the peripheral branches of the pulmonary arterial tree

Following effective treatment of the failing heart the initial acute seizures of pulmonary edema are reversible and the chest x ray markings may assume their previous state Olsson cites experiences with the use of the artificial kidney In a series of sixteen cases treated by control of fluid balance signs of regression of the pulmonary edema were observed in all and in ten the changes disappeared completely After recurring seizures and the establishment of a state of chronic pulmonary congestion the densities became more ill defined the picture changing also as a result of associated pulmonary infarction and low grade infection The densities tend to gravitate to the bases of the lungs which may be obscured by free fluid in one or both pleural cavities If one pleural cavity is involved it is more likely to be the right as is true of mos cases of pleural transudates due to a failing heart

Hydrothorax

Free fluid in the pleural cavity is not often seen during the initial transient seizures of acute pulmonary edema In the presence of pulmonary infarction or left ventricular failure an effusion is often encountered especially in the right pleural cavity The reason for the preponderance of right sided hydrothoraces in advanced heart failure has provoked considerable discussion According to Dock the venous blood in the lungs must return to the left ventricle which has its center of mass near the ventral chest urfaces and the diaphragm slightly to the left of the midline Because of the effect of gravity on this flow Dock estimates that the venous pressure at the bases expressed in its equivalent of water is 20 to 30 cm greater than that of the apex of subjects in the orthopneic position When the patient is in the right recumbent position frequent with cardiac patients the venous pressure in the lateral and basal parts of the right lung is 10 to 20 cm higher than that in any part of the left lung These factors he believes are of paramount importance in explaining the frequency of basal pulmonary edema and of right sided hydrothorax in cardiac failure since the formation of tissue fluid increases rapidly with the rise in venous pressure

In studies by White and co workers also McPeak and Levine several explanations are given for the preponderance of right sided hydrothoraces in congestive heart failure which have many features in common In addition to the anatomic and hydrostatic factors described by Dock it is pointed out that pulmonary lymphatic drainage takes place almost entirely through the right lymphatic duct so that in the presence of lymphatic stasis especially in the right lateral recumbent position capillary leakage is augmented The nature of the heart condition does not seem to have any bearing on the side where the fluid accumulates In a study by White and co workers fifteen cases showed unilateral right hydrothorax and thirteen showed unilateral left hydrothorax Of the thirteen with *left* hydrothorax complete obliteration of the right pleural cavity was present in twelve and unilateral left pulmonary infarction in the remaining case In contrast only four such complicating factors were present among the fifteen unilateral *right* hydrothoraces In other words

if a left-sided hydrothorax is present, the reason the right side is spared is because there is no space for the accumulation of fluid in the right pleural cavity

The chest x-ray findings in hydrothorax complicating cardiac disease do not differ from other types of pleural effusions Of particular interest, from the viewpoint of differential diagnosis, is the rare occurrence of a localized interlobar effusion which may simulate a "vanishing" tumor The exact delineation of interlobar effusions requires lateral, oblique as well as posteroanterior projections The encysted collection of fluid occurs with few exceptions in the horizontal fissure of the right lung In two of five patients with such interlobar effusions, Weiss and co-workers found at autopsy that the cause of the localization of the fluid was due to an obliterative pleurisy of part or all of the remaining pleural cavity The presence of signs of cardiac decompensation, pulmonary congestion and the rapid disappearance of the mass after the institution of treatment, are major points in the differential diagnosis of loculated effusions from pulmonary neoplasms, pneumonias and other intrinsic diseases Higgins and co-workers found reports of thirty-six well documented cases of interlobar pleural effusions due to congestive heart failure, and added six of their own, making a total of forty-one Twenty-six were located in the right transverse fissure and another six in the right oblique fissure These investigators believe that one of the reasons for the preponderance of right-sided loculations of fluid is because they are more readily discovered at this site in routine posteroanterior chest x-rays

Cavernous Hemangioma of the Lung

Clinical Features

In 1932, Reading reported the case of a patient who had cyanosis, digital clubbing and polycythemia associated with congenital telangiectasis of the lung The patient died of a brain abscess Four years later, Bowers reported the case of an infant with a pulmonary hemangioma who died of a fatal hemorrhage the second day after birth These reports, published in state medical journals, escaped general notice until Rodes, in 1938, drew attention of the medical profession to the occurrence of cavernous hemangioma of the lung with secondary polycythemia Following this report, increasing numbers of reports appeared in the literature In 1949, Yater, and Griffin reviewed the world literature and collected forty-five known cases Five years later, Weiss and Gasul reviewed 149 case reports, including two of their own and three unpublished cases The condition has been described under several terms arteriovenous fistula, arteriovenous aneurysm cavernous hemangioma and congenital telangiectasis of the lung

Cavernous hemangioma of the lung is a congenital, at times, familial malformation closely allied to hereditary hemorrhagic telangiectasis (Osler) sometimes found in the skin, mucous membranes and other organs Baer and co-workers found that in 50 per cent of the reported cases of cavernous hemangioma of the lung other vascular abnormalities such as telangiectasis, capillary hemangiomas and spider nevi were exhibited The cases reviewed by Weiss and Gasul included four in which numerous small arteriovenous fistulas were present rather than a single saccular dilatation Moyer and Ackerman reported a family with hemorrhagic telangiectasis of which two members had pulmonary hemangiomas The hereditary feature of the disease was exceptionally well illustrated in another family in which the mother and son had pulmonary fistulas and in another member a probable pulmonary fistula with rupture and death Of thirty-six members of this family whose histories were available, seven had signs of hereditary hemorrhagic telangiectasia and an additional four persons may have been affected (Heyde)

The pulmonary defect consists of a collection of thin walled sacs made up of distended blood vessels The resulting arteriovenous communication allows admixture of venous and arterial blood causing variable degrees of anoxia The severity of the latter depends on the amount of unoxygenated blood passing through the fistula

White estimates that approximately 30 per cent of the blood must be shunted before cyanosis becomes manifest in otherwise healthy individuals

The symptoms and signs of cavernous hemangioma of the lung vary widely The condition may be discovered accidentally in the course of a routine chest x ray survey In others, there may be signs of anoxia as evidenced in dyspnea, cyanosis, polycythemia, clubbing of digits, weakness, dizziness, fainting spells, headache, epileptic fits and transitory paralyses Additional manifestations include hemoptysis and a bruit Depending on the size of the arteriovenous communication there may or may not be cardiac enlargement Following extirpation of the aneurysm there is a decrease in the size of the heart Cavernous hemangioma of the lung may be mistaken for congenital heart disease and occasionally for polycythemia vera Cases have been reported of cavernous pulmonary hemangioma in association with pulmonary artery aortic septal defects and other malformations Maier and co-workers reported an instance of bacterial endocarditis superimposed on an arteriovenous aneurysm

Roentgenology

The roentgen findings of cavernous hemangioma are fairly characteristic provided the possibility of the existence of the condition is kept in mind in patients showing one or more localized densities in the lung, the nature of which cannot be determined by conventional means, especially if evidence of anoxia is present The hemangioma may appear as a compact group of small infiltrations presenting a "comet"-like appearance More often, one sees several fairly large, irregular lobulated densities in the mid or lower portions of a lobe, the entire mass being connected to the hilar vessels by one or more linear bands During fluoroscopy the density may be shown to vary in size with changes in intrathoracic pressures This is accomplished in the following manner With the mouth closed and the nostrils occluded, the patient is told to exhale (Valsalva maneuver) and then to inhale (Muller's maneuver) By these maneuvers the intrapleural pressure is first raised and then lowered thereby causing a decrease and then an increase in the size of the mass

Sectional roentgenography and angiocardiography, especially the later, are decisive in delineating a pulmonary hemangioma and its vascular connection with the hilar blood vessels In a series of nine cases, Steinberg and McClenahan found the classical symptomatology in only one In three instances, the patients had no symptoms, in two the pulmonary arteriovenous fistula was an incidental finding and, in the remaining two, acute cerebral conditions were the presenting symptoms These investigators believe that the diagnosis of arteriovenous fistula can often be made by conventional roentgenography if the index of suspicion is high The diagnosis is established by angiocardiography

In 1939, Smith and Horton described the first case of pulmonary hemangioma in which a diagnosis was made clinically In recent years the diagnosis has been made quite often and confirmed by operation Shenstone is credited with the first successful pneumonectomy for the removal of a cavernous hemangioma The case had been previously diagnosed by Hepburn and Dauphinee Of the total of sixty-six reported cases, slightly more than half have been treated surgically, the majority successfully The following case is reported through the courtesy of Dr Alfred Goldman

Case 31 Male—Age 26

In 1939 the patient was examined by a physician and he was told that he might have leakage of a heart valve A chest film revealed no abnormalities In 1942 the patient was rejected by the Army during the course of a routine preinduction examination because of a shadow in the left lung About this time the patient began to note clubbing of the fingers and cyanosis of the nail beds and lips at first present only on exertion but which soon became constant Later the patient developed frequent nose bleeds Two months prior to admission to the hospital the patient was in an altercation and suffered an injury to the face During the course of his hospitalization due to this injury, the patient had a chest film taken and he was found to have a lesion in his left upper lung field also a murmur in the left chest and other findings consistent with

the presence of an arteriovenous shunt It was because of this that the patient entered Barnes Hospital for further treatment and diagnosis

Physical examination on admission disclosed a marked plethora to the face cyanosis of the mucous membranes marked clubbing of the fingers and toes with a cyanotic hue to the nailbeds A few hemangiomata were noted over the face and on the anterior and posterior aspects of the chest The lungs were clear to percussion and auscultation The *heart did not appear to be enlarged and there was a* normal sinus rhythm There was a loud rumbling grade 3 pre systolic murmur heard at the apex transmitted laterally and into the back This was associated with a mild diastolic component The second pulmonic sound was considerably louder than the aortic second sound The abdomen was negative The routine laboratory data revealed normal urinalysis The red blood count was 6 7 million with 21 grams of hemoglobin and the white blood count was 7 350 cells with a normal differential The red blood cells and platelets appeared normal The blood type was group O RH positive The ECG was interpreted as being normal

X ray examination of the chest including routine kymography revealed a roundly lobulated density in the left midlung field measuring 5 by 5 centimeters There were numerous areas of radiolucency within the density and demonstrated by laminography Medial to the mass there were several large pulmonary vessels leading from the left hilum directly toward the medial border of the mass (Figures 65A B and C) There were marked pulsations at the medial border of the mass and almost no pulsations on its lateral border suggesting the possibility of arterial pulsations medially and the venous channels laterally Intravenous angiocardiography was carried out using 50 cc of 50 per cent diodrast in the right antecubital vein The dye was seen to pass through the branches of the left pulmonary artery into the round lobulated mass noted previously in the left midlung field There was a pudding of dye in this area (Figure 65D) The collection of abundant dye in the rounded shadow with evidence of both arterial and venous bloods indicated an arteriovenous aneurysm No other abnormalities were noted

On August 16 1950 a left exploratory thoracotomy was carried out and a mass measuring about 8 x 5 cms was found in the pectoral segment of *the left upper lobe over which a possible thrill* could be elicited There was marked superficial collateral circulation in the region of the mass as well as overlying the pericardium and mediastinum The fissure between upper and lower lobes was well identified and accordingly with little or no difficulty a left upper lobectomy was carried out which completely excised the mass and caused a marked reduction in the remaining pulmonary vessels in the hilar region No more thrill was palpable after removal of the left upper lobe The patient did exceptionally well postoperatively The removed specimen was reported as a left upper lobe of the lung containing an arteriovenous fistula All efforts were made to keep this patient well hydrated postoperatively and after the second postoperative day the patient was able to take all necessary fluid by mouth without parental aid The wound healed per primum On the first postoperative day the hemoglobin had dropped to 18 gms the red blood count to 5 5 million By the third postoperative day the hemoglobin had dropped to 13 2 gms Associated with this reduction in the polycythemia there was also noted a marked regression in the previously noted cyanosis of the mucous membrane No change was noted in the clubbing of the digits The patient was discharged on the twelfth postoperative day The discharge diagnosis was arteriovenous fistula of the left upper lobe and hereditary hemorrhagic telangiectasia

Pulmonary Embolism and Infarction

Although thromboembolism and infarction are part of the same basic disturbance and often described under one heading the two are not synonymous since thromboembolic phenomena need not necessarily be associated with lung lesions In practice however the symptoms which often alert one to the presence of the vascular disturbance are those referable to the pulmonary infarction Pulmonary artery thrombosis in situ is rare and the effects of such blood vessel obstruction are clinically indistinguishable from embolization arising in the heart or the venous system

Etiologic Considerations

Pulmonary embolism is increasing in frequency The condition is likely to grow in importance as the population ages Various theories

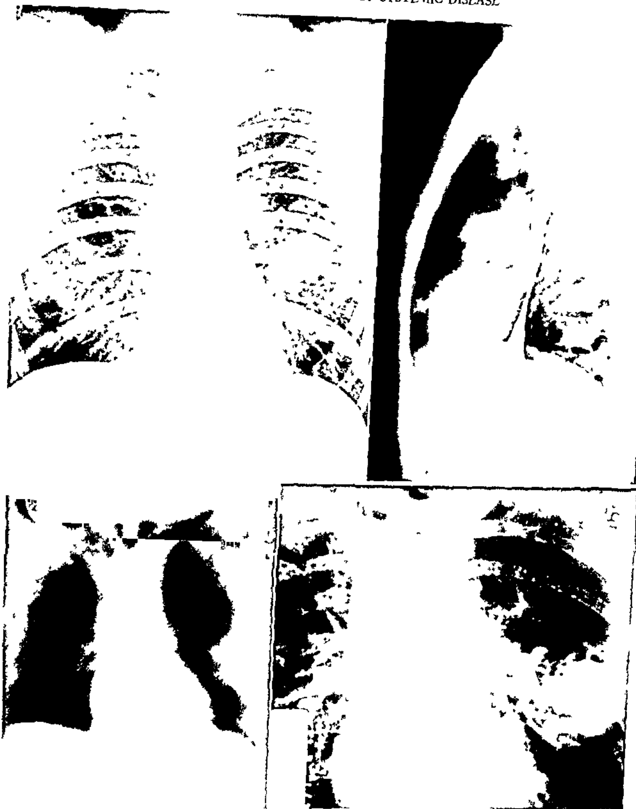


Figure 65 *Case 31* Cavernous hemangioma of lung A, B and C (*Upper left and right, lower left*) Rounded, lobulated density in left midlung, indistinct connections with hilar structures D (*Lower right*) Angiocardiography reveals dye in lobulated mass, also dye filled channels communicating with hilar vessels (Courtesy, *Dr Alfred Goldman, St Louis, Mo*)

have been proposed to explain the increasing incidence of the disorder including such factors as the large number of elderly persons being subjected to major operations and the mounting number of victims to industrial and automobile accidents These several causes and the prolonged bed confinement which the injuries entail favor stasis of the venous circulation thrombosis and emolism

It has been estimated that pulmonary embolism is found in approximately 2 5 per cent of necropsy material and causes 6 per cent of all postoperative deaths The incidence of pulmonary embolism depends to a large extent on the nature of the material studied Towbin surveyed the incidence of pulmonary embolism in an elderly institutional population including 512 cases examined at autopsy The study brought out the importance of age sex and periods of enforced rest A greater incidence was found among women Of the 512 cases examined at autopsy thromboembolic lesions were present in the lungs in 132 or 25 7 per cent In those seventy years of age or over embolism was present in the lungs in 34 per cent Fowler and Bollinger also found fatal pulmonary emboli to occur most commonly among patients with medical gynecologic genitourinary and general surgical services in that order and rarely in obstetric cases The most common predisposing factors found were cardiac disease venous thrombosis dehydration and immobilization These investigators found in their study the heart to be the site of origin in 52 8 per cent and venous thrombosis in 47 2 per cent of all the fatal cases

The close relationship existing between disease of the veins especially those of the lower extremity and embolism is well known Thrombophlebitis of superficial veins rarely gives rise to serious complications for the reason that the inflammatory thrombus is firmly adherent by a local reaction in the wall of the vein The lowest incidence of emboli occurs in migratory phlebitis in which the lesions are limited to small superficial veins the disease being largely perivascular On the other hand quiet thrombosis or so-called phlebothrombosis in which the infectious element and the damage to the vessel wall are considerable is much more dangerous because the loosely attached clot is able to float away in the blood stream and enter the heart and lungs In the absence of heart disease nearly all emboli arise from blood clots in the deep veins of the legs Thrombosis of the veins of the upper extremities head neck and trunk seldom leads to embolism This is supported by the statistics of Barker and his associates also of Henderson The latter studied 189 cases of pulmonary embolism In 86 per cent the sources of embolization were found in thrombosed veins which were direct or indirect tributaries of the lower third of the vena cava

In the case of emboli originating from thrombi in the right side of the heart there is almost invariably present congestive heart failure and often auricular fibrillation Occasionally the thrombus is at the site of a myocardial infarct involving the lateral wall or septum of the right ventricle Mural thrombi in the right side of the heart are a more frequent source of emboli to the lungs than is generally appreciated Approximately one third of adults who die of heart disease are found to have mural thrombi at autopsy The differential diagnosis between acute pulmonary infarction and myocardial infarction is often a difficult one to make The two may coexist In the absence of a clear cut history any acute seizure characterized by severe chest pain dyspnea and tachycardia is apt to be ascribed to acute coronary artery disease and myocardial infarction This is probably the main reason why pulmonary embolism and infarction are so often misdiagnosed

Clinical Features

A blood clot in a pulmonary artery whether caused by a thrombus within the vessel or more often by an embolus from a distant site is one of the dreaded complications of medical and surgical practice The classical seizure occurs in an elderly overweight individual who had recently undergone a major pelvic or abdominal operation A week or ten days after the operation the patient is suddenly seized with severe chest pain dyspnea cyanosis tachycardia faintness sweating vomiting and shock Death may

occur almost instantaneously or after a lapse of a few hours The classical picture is the exception rather than the rule With increasing familiarity with the condition it is possible to differentiate subacute and chronic forms of the disease The latter assume various disguises depending on the nature of the associated pulmonary infarction and bronchopneumonia

The pulmonary infarction which follows embolism gives rise to a train of symptoms and signs which reflect the injury the lung sustains There is cough hemoptysis fever chest pain and leukocytosis The patient may become jaundiced as a result of increase in bile pigment from the extravasated blood in the affected lung which the congested liver is unable to handle The physical signs are characterized by exquisite tenderness of the chest over the affected part of the lung possibly a friction rub and evidence of lung consolidation Free fluid in the pleural cavity is often present

In spite of an imposing number of symptoms and signs which may be encountered in the presence of pulmonary embolism and infarction or possibly *because* of the abundance of such signs few conditions are diagnosed incorrectly as often as pulmonary embolism and infarction The disease has been aptly termed the great deceiver (Wright and Foley) Miller and Berry in an analysis of 104 fatal cases of pulmonary embolism and infarction noted that in only forty four cases was the disease correctly diagnosed In the remainder the clinical diagnosis recorded as the cause of death included congestive heart failure (14) myocardial infarction (6) pneumonia (6) bronchogenic carcinoma (5) and several other conditions In fourteen no diagnosis was made These investigators also draw attention to the fact that the typical picture of pulmonary embolism and infarction is the exception rather than the rule

Owen and co workers reported twelve cases of chronic cor pulmonale and heart failure as a result of multiple and for the most part silent pulmonary emboli Postmortem study revealed the role of widespread organized embolization of the lungs as the only etiologic factor responsible in these patients The study included twelve such cases over a period of twenty years indicating that it is a rare occurrence although the figures are somewhat misleading because the material was selected in order to present the purest form of the syndrome In each patient the dyspnea and cough antedated the appearance of cardiac hypertrophy and congestive heart failure the latter being the cause of death in every case The diagnosis was usually unsuspected The authors believe that a large proportion of cases of so called Ayerza s syndrome result from latent embolization of the lung

Roentgenology

Much has been written on the electrocardiographic changes accompanying embolism especially in cases in which there is sufficient interference with the pulmonary circulation to cause acute cor pulmonale Comparatively little has been written on the chest x ray findings probably because events occur so rapidly that adequate roentgen examinations are seldom obtainable and when chest x rays are taken the bedside product is of such poor quality as to preclude an adequate definition of detail As mentioned previously pulmonary embolism does not always result in infarction of lung tissue This applies especially to large emboli which lodge in a major pulmonary artery death occurring so suddenly that there is no time for secondary effects to register in the lungs Occasionally if the patient lives long enough and it is possible to obtain readable films the chest x ray may reveal features of unusual interest

In 1938 Westermark described certain roentgen findings in lung embolism without infarction which he believed were of diagnostic significance The findings consist of ischemia of the affected lung which reveals itself in a well defined clear zone on the peripheral side of the embolus with diminished or absent vascularization of the part The diminished vascular structure is reflected in an increased radiability of the lung As a result of the distribution of the arterial branches the zone of increased radiability assumes the shape of a wedge with its apex directed toward the hilum and its base toward the periphery of the lung The shape of the wedge

is best seen in the lateral and oblique projections Shapiro and Rigler reported three cases of pulmonary embolism, confirmed at autopsy, which substantiated Westermark's findings Others have been unable to demonstrate such changes

If more precise information were available of the roles played by the pulmonary and bronchial arteries in disease, a satisfactory explanation might be at hand for the contradictory statements of observers relative to the incidence of pulmonary infarction following embolism As indicated in the preceding chapter, the bronchial arteries probably play a minor role in health But, under abnormal conditions, the bronchial arteries may assume certain functions of the pulmonary arteries, as witness the collateral circulation which quickly becomes established between the two systems

Ellis and co workers found that the nutrient requirements of pulmonary tissue distal to an embolus may be supported by the pulmonary arterial circulation through capillary anastomoses in the pulmonary capillary bed They believe that the bronchial arterial circulation is not necessary for this purpose In fact they found that *the bronchial arterial circulation may actually be* a contributing factor to the development of pulmonary infarction after pulmonary embolism since the hemorrhage that occurs into the pulmonary tissue, after pulmonary embolism, may come from the bronchial arterial circulation On the other hand Kjellberg and Olsson claim that the reason for the rarity of finding chest x ray evidence of pulmonary embolism without infarction lies in the fact that no roentgenological changes are observed in the lungs if the circula*tion through the bronchial artery to the part is* undisturbed

In the "typical" case, pulmonary infarction is characterized roentgenologically by a wedge shaped shadow of homogeneous density in one of the lower lobes (Figure 66) At first the shadow is diffuse but after organization it assumes a more homogeneous appearance with sharply demarcated margins It should be emphasized, however, that the "typical" chest x-ray, like the "typical" clinical picture, is the exception rather than the rule In their basic contributions to the subject, Hampton and Castleman have drawn attention to a "hump" sized upper margin of tissues occasionally seen when a costophrenic angle is involved In the process of healing, the infarcts may cast transverse, linear densities (Fleischner lines) which may be confused with "septal" lines or interlobar pleurisy *The diversity of x ray findings are such that* a differential diagnosis is often difficult to make unless one suspects the existence of the condition on the basis of the history and clinical findings, especially the presence of a potential nidus from which an embolism might originate

In most cases a pulmonary infarct presents a picture of bronchopneumonia, obscured by fluid In an analysis of the chest x ray findings of fifty patients with pulmonary embolism and infarction, confirmed at autopsy, Miller and Berry found that only seven showed findings compatible with pulmonary infarct Ten cases were read as pneumonias, seven as congestion, five as pleural effusion, ten as parenchymal abnormalities of one type or another and in eleven the findings were within "normal" limits Among the uncommon sequelae of pulmonary infarction which may reveal unusual chest x-ray findings *are aseptic necrosis and* cavitation of the lung due to bland emboli and, on rare occasion, septic pulmonary infarction

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occur almost instantaneously or after a lapse of a few hours The classical picture is the exception rather than the rule With increasing familiarity with the condition it is possible to differentiate subacute and chronic forms of the disease The latter assume various disguises depending on the nature of the associated pulmonary infarction and bronchopneumonia

The pulmonary infarction which follows embolism gives rise to a train of symptoms and signs which reflect the injury the lung sustains There is cough hemoptysis fever chest pain and leukocytosis The patient may become jaundiced as a result of increase in bile pigment from the extravasated blood in the affected lung which the congested liver is unable to handle The physical signs are characterized by exquisite tenderness of the chest over the affected part of the lung possibly a friction rub and evidence of lung consolidation Free fluid in the pleural cavity is often present

In spite of an imposing number of symptoms and signs which may be encountered in the presence of pulmonary embolism and infarction or possibly *because* of the abundance of such signs few conditions are diagnosed incorrectly as often as pulmonary embolism and infarction The disease has been aptly termed the great deceiver (Wright and Foley) Miller and Berry in an analysis of 104 fatal cases of pulmonary embolism and infarction noted that in only forty four cases was the disease correctly diagnosed In the remainder the clinical diagnosis recorded as the cause of death included congestive heart failure (14) myocardial infarction (6) pneumonia (6) bronchogenic carcinoma (5) and several other conditions In fourteen no diagnosis was made These investigators also draw attention to the fact that the typical picture of pulmonary embolism and infarction is the exception rather than the rule

Owen and co workers reported twelve cases of chronic cor pulmonale and heart failure as a result of multiple and for the most part silent pulmonary emboli Postmortem study revealed the role of widespread organized embolization of the lungs as the only etiologic factor responsible in these patients The study included twelve such cases over a period of twenty years indicating that it is a rare occurrence, although the figures are somewhat misleading because the material was selected in order to present the purest form of the syndrome In each patient the dyspnea and cough antedated the appearance of cardiac hypertrophy and congestive heart failure the latter being the cause of death in every case The diagnosis was usually unsuspected The authors believe that a large proportion of cases of so called Ayerza's syndrome result from latent embolization of the lung

Roentgenology

Much has been written on the electrocardiographic changes accompanying embolism especially in cases in which there is sufficient interference with the pulmonary circulation to cause acute cor pulmonale Comparatively little has been written on the chest x ray findings probably because events occur so rapidly that adequate roentgen examinations are seldom obtainable and when chest x rays are taken the bedside product is of such poor quality as to preclude an adequate definition of detail As mentioned previously pulmonary embolism does not always result in infarction of lung tissue This applies especially to large emboli which lodge in a major pulmonary artery, death occurring so suddenly that there is no time for secondary effects to register in the lungs Occasionally if the patient lives long enough and it is possible to obtain readable films the chest x ray may reveal features of unusual interest

In 1938 Westermark described certain roentgen findings in lung embolism *without infarction* which he believed were of diagnostic significance The findings consist of ischemia of the affected lung which reveals itself in a well defined clear zone on the peripheral side of the embolus with diminished or absent vascularization of the part The diminished vascular structure is reflected in an increased radiability of the lung As a result of the distribution of the arterial branches, the zone of increased radiability assumes the shape of a wedge with its apex directed toward the hilum and its base toward the periphery of the lung The shape of the wedge

is best seen in the lateral and oblique projections. Shapiro and Rigler reported three cases of pulmonary embolism, confirmed at autopsy, which substantiated Westermark's findings. Others have been unable to demonstrate such changes.

If more precise information were available of the roles played by the pulmonary and bronchial arteries in disease, a satisfactory explanation might be at hand for the contradictory statements of observers relative to the incidence of pulmonary infarction following embolism. As indicated in the preceding chapter, the bronchial arteries probably play a minor role in health. But, under abnormal conditions the bronchial arteries may assume certain functions of the pulmonary arteries, as witness the collateral circulation which quickly becomes established between the two systems.

Ellis and co-workers found that the nutrient requirements of pulmonary tissue distal to an embolus may be supported by the pulmonary arterial circulation through capillary anastomoses in the pulmonary capillary bed. They believe that the bronchial arterial circulation is not necessary for this purpose. In fact, they found that the bronchial arterial circulation may actually be a contributing factor to the development of pulmonary infarction after pulmonary embolism since the hemorrhage that occurs into the pulmonary tissue, after pulmonary embolism, may come from the bronchial arterial circulation. On the other hand, Kjellberg and Olsson claim that the reason for the rarity of finding chest x-ray evidence of pulmonary embolism without infarction lies in the fact that no roentgenological changes are observed in the lungs if the circulation through the bronchial artery to the part is undisturbed.

In the "typical" case pulmonary infarction is characterized roentgenologically by a wedge-shaped shadow of homogeneous density in one of the lower lobes (Figure 66). At first the shadow is diffuse but after organization it assumes a more homogeneous appearance with sharply demarcated margins. It should be emphasized, however, that the "typical" chest x-ray, like the "typical" clinical picture, is the exception rather than the rule. In their basic contributions to the subject, Hampton and Castleman have drawn attention to a "hump"-sized upper margin of tissues occasionally seen when a costophrenic angle is involved. In the process of healing the infarcts may cast transverse, linear densities (Fleischner lines) which may be confused with "septal" lines or interlobar pleurisy. The diversity of x-ray findings are such that a differential diagnosis is often difficult to make unless one suspects the existence of the condition on the basis of the history and clinical findings, especially the presence of a potential nidus from which an embolism might originate.

In most cases a pulmonary infarct presents a picture of bronchopneumonia, obscured by fluid. In an analysis of the chest x-ray findings of fifty patients with pulmonary embolism and infarction confirmed at autopsy, Miller and Berry found that only seven showed findings compatible with pulmonary infarct. Ten cases were read as pneumonias, seven as congestion, five as pleural effusion, ten as parenchymal abnormalities of one type or another and in eleven the findings were within "normal" limits. Among the uncommon sequelae of pulmonary infarction which may reveal unusual chest x-ray findings are aseptic necrosis and cavitation of the lung due to bland emboli and, on rare occasion, septic pulmonary infarction.

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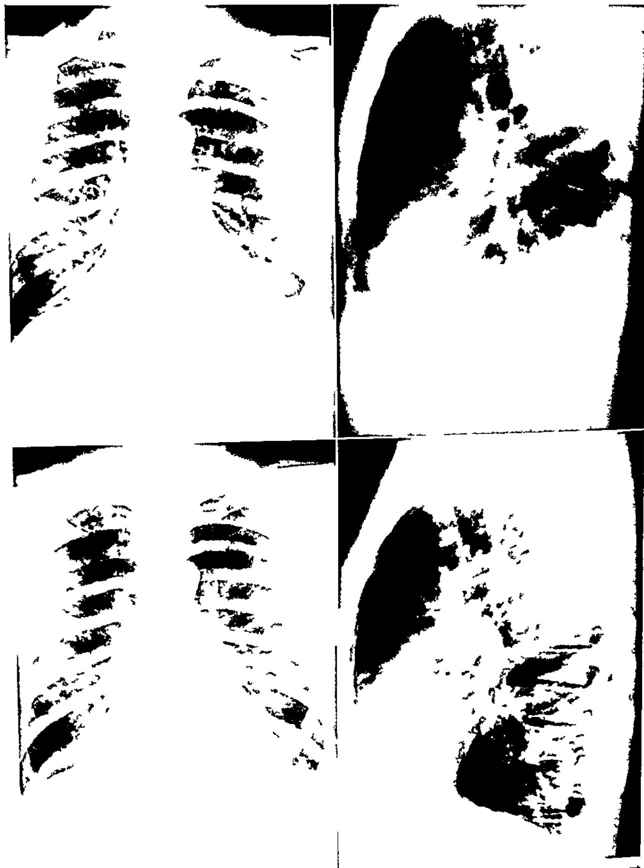
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Figure 66 Pulmonary infarction A (*Upper left*) Irregular densities in left lower lobe, obscuration of left costophrenic sinus increased bronchovascular markings and linear horizontal striations in right lower lobe B (*Upper right*) Left lateral projection shows a roughly triangular density occupying the basal portion of the left lower lobe, encapsulated fluid above diaphragm prominence of interlobar fissure (Sudden onset of chest pain fever signs of consolidation and pleural friction rub over left base) C and D (*Lower left and right*) Six weeks later complete resolution of basal densities except for blunted costophrenic sinuses

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Chapter 12

Diagnosis: The Changing Scene

Introduction

The diagnosis and treatment of pulmonary diseases, and this applies to other diseases as well, changes with the times. In addition to matters of immediate concern to the patient, to be discussed shortly, the well informed physician has to be aware of certain environmental factors which may also have a bearing on the problem, although indirectly. The physician needs to keep abreast of changing fashions of medicine, the implications of an aging population, of the changing incidence and pathologic picture of certain diseases, also the current status of new man made diseases. Even advances on the socio economic front, including the increasing use of chest x rays, the rapid development of disease detection clinics and the increasing facilities available for hospitalization of the sick or supposed sick, carry with them certain repercussions relating to the diagnosis and treatment of disease.

Changing Fashions in Medicine

Sosman makes some pertinent comments to the effect that a physician's approach to a problem is largely conditioned by what he has been taught and the mode of thought in his immediate environment. Currently the laboratories and scientific instruments are playing the major role. The concept of gross pathology as the basic disturbance underlying disease processes and the production of symptoms has been relegated to the background. This is the metabolic biochemical electrolyte era. As a forceful illustration of this new approach to medicine I recently heard a young physician state in all seriousness that a patient under his care had died in electrolyte balance. It brings to mind the macabre jest of yesteryear when a patient with acute pneumonia under oxygen was said to have died with pink cheeks.

It is true that most of the conditions described in these pages require laboratory tests in establishing a diagnosis and in following the course of treatment, often elaborate procedures available only in well equipped institutions. But the first step in approaching a problem is looking at and talking to the patient and seeing the latter as a distressed person in an unhappy environment rather than as a biochemical phenomenon. This faculty is acquired by the physician in the clinic and at the bedside, not at the laboratory table. The current surge in importance of psychiatry as a major discipline of medical education promises to serve as an instrument of teaching the physician the importance of dealing with the patient as a person regardless of the nature of the disease of which he may or may not suffer.

Implications of an Aging Population

Since 1900 the number of persons over sixty five years of age in the United States has quadrupled, those in the age group from forty five to sixty four has tripled. It is estimated that within a decade or two the average span of life for the population of the United States may reach seventy years, approximately one third composed of people over forty five years of age. Insofar as it pertains to intrathoracic diseases one may expect that, as the population structure shifts to the elderly, physicians will encounter an increasing number of patients with degenerative lung diseases including fibrosis and

emphysema granulomatous lesions neoplasms as well as pulmonary manifestations of cardiovascular and systemic disturbances

In addition to the changes in the lungs the aging chest is accompanied by physiologic alterations in the thoracic cage itself which may be mistaken for pathologic processes within the lung parenchyma Evans has drawn attention to some of the modifications that occur in thoracic structures in the process of aging A small shrunken breast in an aged female may simulate malignant metastatic disease Pronounced arthritic changes in a circumscribed portion of the spine may appear as an abnormal mediastinal density A tortuous aorta may be mistaken for a pulmonary neoplasm This applies also to a buckled innominate artery due to elongation or dilatation of the vessel An enlarged pulmonary artery especially on the right side may cause an undue prominence of the root shadow

Implications of the Changing Character of Diseases

Preventive measures and antimicrobial treatment have brought about a dramatic decline in the incidence of the acute pneumonias The reduced incidence of this disease is reflected not only in daily practice but also at autopsy Cannon almost bemoans the fact that our residents and medical students now learn about the pathologic aspects of lobar pneumonia only from books from the reminiscences of older clinicians and pathologists and from museum specimens As a result of the reduced incidence of the acute pneumonias there is a diminishing number of postpneumonic empyema and bronchiectasis The decline of tuberculosis has relegated this one time scourge of mankind to a secondary place among major killers How long will it be before the captain of the men of death follows the fate of pneumonia only time will tell At present an elderly person who presents himself with cough or a change in the quality of the cough or an atypical pneumonia or blood spitting is more likely to bring to mind the possibility of the underlying cause being a pulmonary malignancy rather than tuberculosis

Implications of Changing Forms of Treatment

Present day knowledge is not sufficiently advanced to assess the role which the widespread use of chemotherapy and antibiotics are playing in changing the pathologic pattern of infections Cannon quoted previously points out that one time lethal diseases such as lobar pneumonia purulent meningitis, *mastoiditis puerperal sepsis* septicemia and venereal diseases have either been rendered innocuous or practically abolished These diseases have gradually vanished from the necropsy room so that life in the morgue has become correspondingly placid The once common terminal pneumonia the friend of the aged is now so seldom seen that at times one wonders about the mounting therapeutic obstacles to the very act of death itself

As serious microbial infections are being encountered less often there is an ever increasing number of resistant strains of bacteria developing as a result of antimicrobial therapy Current interest centers on the development of superimposed infections due to antibiotic suppression of drug sensitive microorganisms One is confronted with increasing numbers of pulmonary infections caused by fungi especially monilia staphylococci and of pseudomonoas and proteus types resistant to antibiotics Of late discerning surgeons are becoming less dependent on antibiotic umbrellas and more on meticulous surgical technique Penicillin and other potent antibiotics are being reserved for rainstorms rather than for summer showers (Bitten)

The emergence of drug resistant acid fast bacilli as a result of prolonged use of streptomycin para aminosalicylic acid and isoniazid in the treatment of tuberculosis is a problem the ramifications of which are still to be determined Recent communications from several centers where large numbers of tuberculosis patients are on ambulatory treatment are revealing an increasing incidence of tuberculosis in infants as a result of contact infection at home Of particular significance is the fact that cultures obtained from the gastric contents and spinal fluids of these infants are showing a decided increase

in strains of tubercle bacilli which are resistant to antituberculosis drugs.

The widespread use of potent antimicrobial agents may also be a factor in the rising incidence of diffuse interstitial pulmonary fibrosis of undetermined etiology. As indicated in Chapter 6 it is suspected that the increasing incidence of diffuse interstitial fibrosis may be due in part to premature organization of pulmonary exudates as a result of the widespread and often indiscriminate use of potent antimicrobial agents. There appears to be also an increase in the incidence of disseminated lupus erythematosus, scleroderma, dermatomyositis, polyarteritis nodosa, rheumatoid states and other disturbances of the so-called collagen group of diseases. To a major degree this increase is only apparent because of timelier recognition of these diseases and the diagnostic help furnished by newer tests. But in part the increase may be due to the allergic reactions which often accompany sulfonamide and antibiotic treatment. Barr has drawn attention to the fact that the history of new drugs indicates that not all their potential dangers are immediately apparent, also that recently drugs have been introduced for specific purposes that may actually produce complete syndromes.

Studies on the late reactions to hypotensive drugs indicate that a new man-made disease is on the horizon. Dustan and co-workers reported on a group of patients under prolonged hydralazine (Apresoline) treatment who presented an unusual rheumatic and febrile syndrome characterized in its milder phase by rheumatoid arthritis and in its severer form by symptoms of acute systemic lupus erythematosus including the occasional finding of L.E. cells. Of particular significance from the viewpoint of the present discussion is the occasional occurrence of unexplained pneumonitis as well as pleural and pericardial effusions which can be controlled with ACTH and cortisone. The hydralazine syndrome which simulates a collagen disease occurs in about 10 per cent of patients treated with the drug.

Morrow and co-workers reported on the side effects of a combination of 1-hydrazinophthalazine and hexamethonium chloride (Hyphex) used in the treatment of 250 patients with hypertension. Among the side effects these investigators also found a number of patients with transient arthralgia indistinguishable at first from acute rheumatoid arthritis and after prolonged treatment from disseminated lupus erythematosus. Among the patients who died there were eight deaths due to apparent pulmonary complications. The findings in five were those of an interstitial pneumonitis rapidly progressing to death without the development of chronic cor pulmonale. The picture was in keeping with that described by Hamman and Rich. Morrow and co-workers comment on the fact that since they were able to add a significant number of cases to the fourteen previously collected from the literature by Kahn, Peeler and myself, it would indicate that the interstitial pneumonitis probably introduced by the therapy is a new disease chemically produced.

Barr introduces his timely discussion on the hazards of modern diagnosis and therapy with the quotation: First of all be sure you do no harm. *Primum non nocere.* In other words, if in doubt of the diagnosis it is safer to withhold potentially dangerous agents.

Diagnosis

Clinical History

Next in importance to the chest x-ray in the diagnosis of pulmonary disease is the clinical history. In his haste for objective findings the busy physician sometimes fails to listen to the patient's complaints. But the more experienced the physician the more time he takes in asking questions and less in thumping the chest. He has learned that a provisional diagnosis can often be made on the basis of the history alone. As Bird aptly remarks: Of all the technical aids which increase the doctor's power of observation none comes even close in value to the skillful use of spoken words—the words of the doctor and the words of the patient.

I recently had under observation a woman of fifty who showed in the chest x ray irregular but somewhat circumscribed densities in the right lower lobe, also infiltrations in the lingula (Figure 67A). Sarcoidosis, neoplasm and inflammatory disease were suspected but a diagnosis could not be established in spite of thorough studies including bronchoscopy and scalene node biopsy. At one interview, the patient offered the information which I should have obtained by direct questioning that for a period of fifteen years she had been taking at bedtime a mouthful of *mineral oil directly from a gallon bottle, "it was cheaper by the gallon."* It was not difficult to ascertain the fact that on many occasions she gagged, especially when the bottle was full and top heavy. Obviously, in the course of years variable amounts of mineral oil had been aspirated into the lower air passages and caused a chronic pneumonitis. A chest x ray taken several years previously became available and it showed similar infiltrations.

Oil aspiration or lipid pneumonia is a frequent occurrence in debilitated persons who because of the presence of cardiospasm, neurologic or cancerous disturbances are unable to swallow properly, thereby allowing oily medication to enter the larynx and lungs. Even healthy individuals may develop lipid aspiration pneumonia as a result of energetic self medication with oily *nose drops or laxative oils.*

Good history taking requires skill, tact and knowledge on the part of the physician. Skill in asking leading questions without seeming to stress their importance, tact in allowing the patient to "blow off steam" and knowledge in evaluating the significance of various complaints. "Successful talking with patients, contrary to common opinion, is more a science than an art and a good bedside manner is a myth unless it has its roots in scientific understanding" (Bird).

In most instances an adequate history can be obtained in a short time, occasionally considerable time is necessary. A fortuitous remark may throw an entirely different light on a seemingly perplexing problem. Taking a history cannot be relegated to a secretary. How the patient answers is as important as what is said. In obtaining a history it is well to bear in mind that placid individuals are apt to minimize their complaints, high strung individuals magnify them. Constant interruptions on the part of the examiner and undue harping on a few symptoms may cause the patient to give *misleading information for fear* that his intelligence is being questioned. After repeated questioning any audible sound in the chest may become a wheeze, a sensation of cold a chill, a slight chest discomfort, an excruciating pain, streaked sputum, a mouthful of blood.

If the onset of the disease is recent and relatively acute, and events are fresh in the patient's mind, the history elicited is usually reliable and the physician has little difficulty in reconstructing a complete sequence of events. If the illness is of long duration and of low-grade intensity, the physician may have to do considerable probing. If there is a family history of tuberculosis it may be difficult to elicit this fact, especially if the patient is being interviewed in another's presence. The mere fact that a person had been ex*posed to tuberculosis does not necessarily indicate* that tuberculosis is the cause of the complaints. More often it is not. Adequate histories are also difficult to obtain in patients with pulmonary infections following alcoholic intoxication.

Difficulties in obtaining reliable histories are particularly great in the case of patients who have *had treatment for psychiatric conditions. In one patient,* under my care, the presence of considerable pain in the left upper chest and a circumscribed density in the upper aperture of the thorax seemed in keeping with a malignant neoplasm (Figure 67B). A thorough study, including bronchoscopy, was unrevealing. After considerable probing, the husband offered the information that he had noted the wife's breath had been offensive at times. A history of foul odor to the sputum had been sought for but had not been obtained previously probably because the patient had been receiving penicillin and was not expectorating. Additional questioning soon *established the fact that the patient had* recently received shock treatment for a depressive state. The chest x ray taken prior to the shock treatment was then obtained and it showed no abnormalities. Obviously one was dealing

with an aspiration lung abscess After several months intensive penicillin treatment the lesion resolved completely

The fact that the symptoms may be of recent onset does not necessarily imply recently acquired disease The present illness may be due to an exacerbation of a long smoldering focus This applies especially to tuberculosis Furthermore the mere fact that an individual has had the disease for a comparatively long time does not rule out the possibility that one is dealing with a malignant neoplasm Bronchiogenic carcinoma may evolve over a period of several years and not come to light until late in its evolution Finally the fact that a patient has acute symptoms referable to the chest does not necessarily indicate that the disease found in the chest is the cause of the symptoms An acute respiratory infection often prompts the physician to take a chest x ray and a silent neoplasm tuberculosis or other condition discovered in this manner Children are often admitted to hospitals with acute respiratory symptoms The obtainment of a positive tuberculin test and evidence of a primary tuberculous infection in a lung in the chest x ray is often a matter of concern Almost invariably the acute respiratory symptoms turn out to have had nothing to do with the finding of the tuberculous infection usually inactive or undergoing arrest

Of interest in the past personal history of a patient is information relative to the country of birth in the case of immigrants or sojourns in distant parts of the world in the case of native born It is also important to inquire of the patient s recent travels in the United States as well as in foreign countries where certain diseases are endemic and which may affect the lungs Parasitic infections acquired in the course of travel often present difficulties in diagnosis Immigrants from the Mediterranean basin may harbor

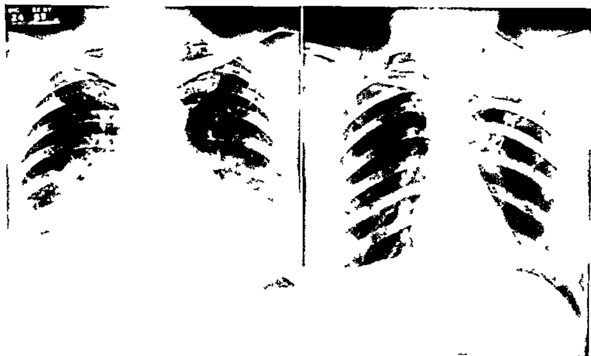


Figure 67 ... Irregular densities and reticu lations i ... lower lobe (Lipid aspiration pneu monia due ... t) Dense circumscribed infil tration in ... chest Sputum examinations failed to ... ng history obtained of sh ck treatm ent ... Resolution of density after



Figure 68 Pulmonary coccidioidomycosis A (*Left*) Thin walled cavity in left upper lobe moderate degree of surrounding infiltration linear density at base of right upper lobe (*Resident of Arizona history of cough and bloody expectoration tuberculin skin test negative coccidioidin test positive coccidioides immitis organisms present in sputum*) Pulmonary histoplasmosis B (*Right*) Miliary calcifications evenly distributed throughout both lungs (Initial chest x ray at age of fourteen years revealed scattered soft infiltrations at the age of twenty two infiltrations underwent calcification as noted Tuberculin skin test negative histoplasmin positive) (Courtesy Dr H G Zwerling Berkeley Cal)

echinococcal disease which may simulate pulmonary tumor Brucellosis is found in certain parts of the United States as well as in Europe and South America Various *parasitic infections* were acquired by the Armed Forces in the Far East during World War II In the United States *coccidioidomycosis is concentrated chiefly in* California and Arizona (Figure 68A) histoplasmosis in the Eastern Central and Midwestern states (*Figure 68B*) *Both* may give rise to pulmonary disease Space does not permit of a more extended review of the subject

It is also essential that information be obtained of operations recently performed under general anesthesia or recent tooth extractions and tonsillectomy Berson and Adriani have shown that silent regurgitation and aspiration of gastric contents leading to pulmonary infection may occur even during smooth endotracheal anesthesia the anesthetist being unaware that such had taken place In difficult inductions the incidence of regurgitation and aspiration is considerably greater than that occurring during smooth inductions

Although diseases of infancy and childhood may attack adults and vice versa there is a definite age and seasonal incidence of certain respiratory infections the knowledge of which is important in diagnosis The common cold *influenza and pneumonia are infrequent during the* warm months, the number of cases begins to increase thereafter reaching a peak in January *Influenza is a disease of cold weather The* Spring months favor infection with the coccus group of bacteria Congenital malformations are occasionally the cause of acute respiratory distress in the newborn Developmental defects may remain latent and manifest themselves in later years as a result of repeated lung infections Such defects may occur in several members of the family The association of transposition of the viscera with sinusitis and bronchiectasis so called Kartagener s syndrome is being reported with some frequency Areal described four instances in one family of total visceral inversion with congenital bronchiectasis and cystic lung The occurrence of familial hemorrhagic telangiectasis associated with pulmonary arteriovenous fistulae has been discussed in Chapter 11 Bronchopneumonia in children may complicate acute contagious diseases notably measles and whooping cough Bronchiectasis in later life may occa

sionally be traced to such episodes On the whole, the school age is fairly immune to serious lung disease

The adolescent girl and young woman is susceptible to tuberculosis although the disease is now being discovered with greater frequency in older age groups Adulthood is the age in which pneumonia is most prevalent A failing heart is a frequent cause of symptoms referable to the chest, the first evidence of cardiac decompensation often being a hacking cough and basal rales Chronic bronchitis and nonspecific bronchopulmonary infections are more frequent with advancing age Many elderly individuals with chronic pulmonary fibrosis and bronchiectasis developed their diseases during the pandemic of 1917-1918 Some trace their "lung trouble" to inhalation of noxious gases during World War I Bronchiogenic carcinoma, as mentioned is now the most frequent serious lung disease of middle and advancing age, particularly in the male Upper lobe fibroid tuberculosis associated with emphysema often masquerades as chronic bronchitis The fact that a patient has, or is known to have had, pulmonary tuberculosis does not exclude the presence of a malignant pulmonary neoplasm The occurrence of the latter in patients who had been treated many years previously for tuberculosis is not at all rare (Figure 69)

With respect to occupational lung diseases, it should be noted that silicious dusts may continue to exert their deleterious effects long after the individual has broken contact with the irritant (Figures 70A and B) Organic dusts such as fur, feathers, cotton and wool, although they may not cause demonstrable disease in the chest x ray, are often the cause of chronic cough In view of the increasing incidence of carcinoma of the lung, it might be well to point out that certain occupations predispose to the development of malignant pulmonary neoplasms The carcinogenic effects of smoking on the lungs is well documented In puzzling cases, the information that the patient had been a heavy smoker for many years is often sufficiently impressive to swing the balance in favor of the condition being carcinoma rather than some other cause In suspected carcinoma in the female, the fact that the patient had been a nonsmoker carries considerable weight in excluding carcinoma because of lower incidence of the disease in the female sex in general Among occupational hazards, it should be noted that workers exposed to inhalations of chromate dust or pigment, asbestos dust and radioactive substances have a higher incidence of carcinoma of the lung than do workers in other occupations

Before concluding this section, a few remarks on the psychosomatic aspects of pulmonary disorders are in order One encounters patients, usually women, who complain of "inability to catch the breath" or "a feeling of weight in the chest" or "a lump in the throat" and similar expressions for which no adequate cause can be found Tachypnea, as a form of respiratory neurosis, may end in tetany as a result of hyperventilation A rather frequent occurrence is a loud unproductive cough encountered in patients who may have been told, long proved unfounded, that they harbored some lung disease The constant cough, in itself becomes a source of irritation and a vicious cycle is established One gets the impression that in some of these individuals the cough is a defense reflex which has outlasted the original condition, if there ever was a physical basis It should be emphasized, however, that before one makes a diagnosis of a neuropathic constitution, a chest x ray should be taken and the upper air passages carefully examined

The Physical-X-Ray Examination

It is a daily experience to discover in a chest x-ray evidence of more disease in the lungs than is realized from the patient's symptoms and physical findings But after one has viewed the film, additional data are often obtainable on requestioning the patient and reexamining the chest The appearance of the chest x-ray may prompt the physician to inquire about the individual's occupation, past illnesses, travels and to obtain further information which he might otherwise have neglected to do A blunted costophrenic sinus or a thickened pleura may help in eliciting a history of influenza, pleurisy or pneumonia,

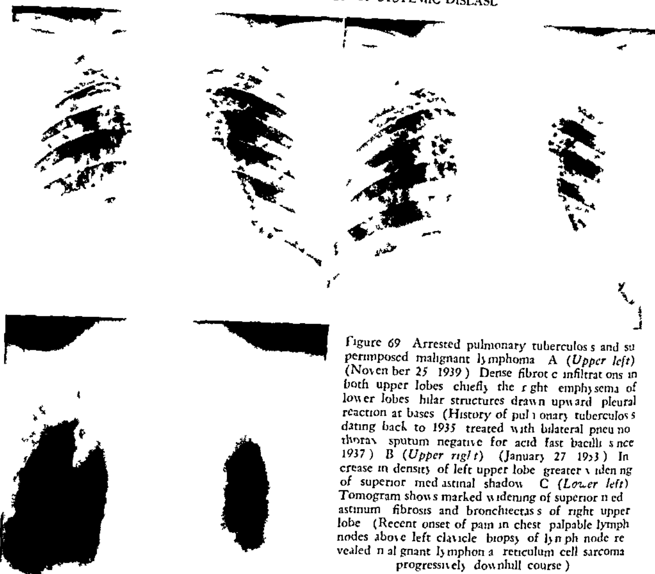


Figure 69 Arrested pulmonary tuberculosis and superimposed malignant lymphoma A (*Upper left*) (November 25 1939) Dense fibrotic infiltrations in both upper lobes chiefly the right emphysema of lower lobes hilar structures drawn upward pleural reaction at bases (History of pulmonary tuberculosis dating back to 1935 treated with bilateral pneumothorax sputum negative for acid fast bacilli since 1937) B (*Upper right*) (January 27 1953) Increase in density of left upper lobe greater widening of superior mediastinal shadow C (*Lower left*) Tomogram shows marked widening of superior mediastinum fibrosis and bronchiectasis of right upper lobe (Recent onset of pain in chest palpable lymph nodes above left clavicle biopsy of lymph node revealed malignant lymphoma reticulum cell sarcoma progressively downhill course)

long forgotten An apical scar may prompt the physician to question about tuberculosis Scattered calcified foci in both lungs may bring out the fact that the person had lived in parts of the country where histoplasmosis is endemic The presence of diffuse pulmonary infiltrations may focus attention to the possible existence of a systemic disease One may encounter an individual momentarily engaged in an innocuous occupation yet the film may disclose stigmata suggestive of silicosis or some other dusty occupation which the patient had forgotten to mention but easily recalled once the matter is brought to his attention

Bearing the aforementioned in mind physicians who have occasion to examine large numbers of persons with suspected lung disease have been following in recent years a somewhat different routine than that generally taught in medical schools After listening to the patient s complaints and examining the chest an x ray is taken and studied Following this preliminary orientation a more detailed history is obtained and a more critical examination made of the chest If necessary, additional chest x rays are taken in various projections to bring out specific details This method of examining persons with suspected lung disease may not be adaptable to the daily

routine of the general practitioner, especially if there is no immediate access to roentgenographic equipment But, in principle the need of integrating the chest x ray within the scope of the physical examination is valid In fact unless this is done the examination is incomplete It is no criticism of the physician if he is unable to arrive at a precise diagnosis of a chest ailment when he attends a patient at home The immediate consideration is the relief of distressing symptoms secondarily the making of a correct diagnosis But the patient should be advised to have a chest x ray taken as soon as he has recovered from the acute illness If the disease shows no signs of abating every effort should be made to have a chest x ray taken at home by portable apparatus

Most textbooks on physical diagnosis have little to say on roentgenology in general much less on ways and means of dovetailing the latter with the physical examination With an offhand suggestion that a chest x ray be taken *when indicated*, the best single means of diagnosing lung disease is relegated to the realm of laboratory procedures and the student is left with an erroneous impression of its real contribution Such correlations as are made between physical signs and chest x-ray findings are more in keeping with postmortem pathology than with incipient disease The reason for the relative neglect of the chest x ray lies in the fact that the principles of physical diagnosis were firmly established long before the introduction of roentgenography and unfortunately, the former has retained its primary position

By and large students of medicine are still being taught signs which have been shown to be incorrect or seldom demonstrable or of questionable value, at best Few teachers of physical diagnosis dare admit that abnormal physical signs if elicited are better appreciated *after* one has seen the chest x ray and reexamined the chest Were this procedure taught to the student

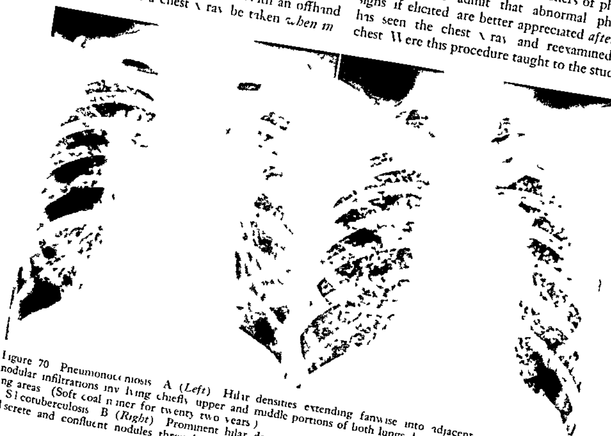


Figure 70 Pneumonoconiosis A (*Left*) Hilar densities extending fanwise into adjacent zones linear and nodular infiltrations involving chiefly upper and middle portions of both lungs hyperillumination of surrounding areas (Soft coal miner for twenty two years) Silicotuberculosis B (*Right*) Prominent hilar densities showing egg shell calcifications of lymph nodes discrete and confluent nodules throughout both lungs, emphysema of remainder of lung (Subway tunnel worker for forty years)

the latter would then be in a position to understand why an area of impaired resonance may be caused by lung consolidation in one patient by a pleural effusion in another by consolidation plus fluid in a third or by some other abnormal state in a fourth The suppressed breath sounds may then be revealed as due to emphysema pneumothorax pleural effusion consolidation or some other space occupying disease The integration of the x ray and the physical findings in the over all examination not only helps to account for the presence or absence of various abnormal conditions which may be encountered in the chest but it also serves to sharpen the physician s diagnostic acumen should a chest x ray not be immediately available

On the other side of the picture should be mentioned the fact that the chest x ray does not disclose all pathologic states which may affect the lungs Under such conditions the elicitation of abnormal physical signs in the presence of an apparently negative chest x ray is in itself of diagnostic value Inflammatory conditions of the tracheobronchial tree unless associated with pulmonary lesions are not demonstrable in the chest x ray although they may be suspected from the history and physical signs Likewise the physical signs may be more informative in the case of viral or chemical bronchiolitis or lesions of the cortical portions of the lungs

Partial occlusion of a bronchus may give rise to a harsh rhonchus or wheeze over a limited area of the chest yet in the routine chest x ray no significant alterations from the norm may be detected The presence of bronchiectasis may occasionally be suspected from the routine chest x ray alone especially if the history and physical signs are also suggestive But in many instances the chest x ray is within normal limits and in no case can an unequivocal diagnosis of bronchiectasis be made without a confirmatory bronchographic examination Emphysema one of the most frequent conditions encountered is easily missed in the chest x ray It is obvious therefore that although the chest x ray broadens the horizon and serves as a check on the physical findings it does not displace the later

One need not belabor the point that if there is one branch of medicine in which the student is in need of being brought up to date it is in the field of diagnosis of chest disease The modern stethescope is a more flexible tube than is the paper cylinder improvised by Laennec but to all intents and purposes the stethescope is still largely a decorative piece rather than a precision tool and possibly a poorer conductor of sounds than the original makeshift Let me hasten to add however that although the stethescope is essentially the hallmark of the physician it is here to stay Folded in the physician s hand or nestling around his neck or even peeking out of his coat pocket the mere sight of the instrument is often sufficient to drive pain away and start the patient on the road to recovery Many a patient has been cured by the venerable family doctor who took time to listen to his woes and applied his ear to the covered chest And not infrequently the old gentleman was somewhat hard of hearing

The diagnosis of chest diseases evolves around the proper use of the chest x ray In conjunction with the history physical signs and pertinent laboratory tests the chest x ray completes a discipline upon which the physician has to depend for a reasonably accurate diagnosis The pulmonary lesions occurring in the course of systemic diseases are usually deep seated and little concrete information may be obtainable not only from symptoms and physical signs but even from chest x rays Often the only recourse is the performance of an exploratory thoracotomy and the obtainment of a lung biopsy But even the availability of the latter may shed little light since all too often the histologic features of the biopsy specimen are in keeping with one of several pathologic states For these reasons the physician has to take into consideration not only what meets the eyes in the way of chest x rays and bioptic material but in difficult situations he must also draw on a broad fund of knowledge of internal medicine

Diagnosis: Symptoms and Signs

Introduction

COUGH, PAIN IN THE CHEST, dyspnea and other symptoms of ill health are individually of little help in differential diagnosis except for drawing attention to the fact that all is not well. But when symptoms occur in certain sequence or in certain combinations, a number of possibilities come to mind. For example, pain in the chest on respiration, associated with dyspnea, *after* a period of cough and bloodspitting suggests a pulmonary disease with secondary involvement of the pleura. On the other hand, pain in the chest, not related to respiration, associated with dyspnea, *followed* by cough and bloodspitting is more in keeping with myocardial infarction and pulmonary congestion. When a patient's complaints are analyzed in the light of the entire case history and chest x-ray findings, the symptoms assume major importance not only in diagnosis but also in prognosis.

Symptoms are caused in part by structural damage of the lungs and in part by functional disturbances with respiration and blood oxygenation. The former are expressed chiefly in cough expectoration and chest pain, the latter, in varying degrees of anoxia, clinically expressed in dyspnea and cyanosis. In addition, there are symptoms of a more generalized nature such as fever, tachycardia, loss of weight and sweating. These need not be considered in detail here but it is well to point out that in the differential diagnosis of systemic diseases such symptoms and signs may be of greater significance than those referable to the chest.

COUGH

Cough is among the first symptoms of lung disease to appear and among the last to disappear.

The character of the cough may suggest site of the disease. A persistent cough, with without an accompanying wheeze, may be allo gic in nature. Hypersensitive individuals are ap to cough for months after the mildest uppe respiratory infections. A persistent postnasal discharge may be the focus. A latent middle ear infection or an hypertrophied uvula should not be overlooked in seeking a cause for unexplained cough, particularly if the latter is of a nonproductive, explosive variety. Patients with mitral stenosis associated with enlargement of the left auricle may cough as a result of elevation and compression of the left main bronchus. Cough is, of course a prominent symptom of decompensated heart disease associated with pulmonary congestion. A dry, spasmodic cough may be among the first symptoms of intraabdominal disease, painful if associated with subdiaphragmatic irritation. A suppressed, painful cough often accompanies regional invasion of lung by carcinoma.

As a rule, the louder and harsher the cough, the more likely is the seat of the disease in the trachea and larger bronchi. A "brassy" cough is occasionally heard if the trachea is compressed by a substernal thyroid, mediastinal neoplasm or an aortic aneurysm. The shorter, deeper and more painful the cough, the more apt is disease to be present in the parenchyma and pleura. Paroxysms of cough occur in bronchial asthma, whooping cough, bronchial obstruction and bronchiectasis. On rare occasion, a fit of coughing may produce unconsciousness with or without convulsions, so-called, laryngeal vertigo or, better termed, cough syncope. Unless the cause is obvious, a persistent cough, especially if asso-

ciated with unilateral wheeze calls for bronchoscopic examination A pulmonary neoplasm foreign body or other evidence of internal or external bronchial compression will often be found Any unexplained cough in a patient of the cancer age deserves attention If the chest x ray shows the slightest abnormalities for which a cause is not readily ascertainable a bronchoscopy is in order

Expectoration

Usually but not invariably expectoration follows cough if the latter continues long enough The cough tends to subside when it becomes productive Women and children who swallow their sputum may eliminate the latter in the vomitus I have encountered several patients with esophageal hiatus hernia in whom an emetic cough was a prominent symptom The gross appearance odor color and quantity of sputum eliminated are to be considered in differential diagnosis but they are not dependable without additional findings Catarrhal conditions of the trachea and bronchi give rise to thin mucoid sputum deeper infections of the lung are associated with thick purulent secretion Frothy blood tinged sputum is often encountered in pulmonary edema viscid dark brown sputum in pneumococcal pneumonia slimy sticky sputum in Friedlander pneumonia Long continued expectoration of purulent sputum mixed with blood is a frequent occurrence in carcinomatous lung abscess The foul odor of anaerobic pulmonary suppuration is a characteristic feature of the disease It should be noted however that the foul odor may be suppressed by antibiotic treatment and that one may harbor a serious lung disease without much if any cough or expectoration

In the presence of upper lobe cavitation there is little variation in the amount of sputum eliminated during the day because of the dependent drainage Cavities situated in the lower lobes retain the secretions during the day when the patient is in the upright position The sputum is eliminated in large amounts immediately on arising or on change of position when the contents of the cavity overflow into the main bronchi and the cough reflex is excited Many patients with chronic pulmonary suppuration learn to control their cough and expectoration and empty the bronchial contents at intervals

Hemoptysis

There is hardly a disease affecting the respiratory tract directly or indirectly which may not cause bloodspitting The dilatation and anastomoses of the pulmonary and bronchial blood vessels in the presence of disease the intimate contact of the capillary bed with the alveoli and the external communication of the bronchi provide an ideal arrangement for bloodspitting The remarkable thing is that the hemoptysis does not occur more often Bloodstreaking may occur during acute lung infections when the affected parenchyma becomes engorged with blood Copious amounts of blood are usually not expectorated due to early thrombosis and occlusion of the blood vessels Except in instances of necrotizing pneumonias gross hemoptysis is uncommon In acute lung abscess the initial symptom may be a profuse hemorrhage the blood mixed with purulent matter

Hemoptysis is encountered much more often in chronic bronchopulmonary than in acute diseases Dilated bronchi or rigid cavities traversed by partially thrombosed blood vessels which have lost the support of the contractile elements of the lung are favorite sites of bleeding Hemorrhage is therefore frequent in bronchiectasis carcinoma chronic lung abscess and fibroid tuberculosis Occasionally the hemorrhage is fatal As might be expected from the age incidence of these diseases hemoptysis occurs more often in older age groups and more often in males A notable exception is bronchial adenoma which is more common in young women In the presence of caseous tuberculosis and other infectious processes associated with considerable discharge hemoptysis is particularly dangerous because it predisposes to spread of the disease to uninvolved parts of the lungs

It is often difficult to ascertain even at autopsy the site of the pulmonary bleeding In bronchiectasis and malignancies affecting major bronchi

the bleeding usually originates in one of the bronchial arteries Ulcerative diseases especially tuberculosis are more apt to involve branches of the pulmonary artery The pulmonary veins are rather small until they reach the hilus and it is doubtful whether they give rise to significant bleeding Bloodspitting occurs in the course of cardiac diseases associated with hypertension and arteriosclerosis of the lesser circulation Mitral stenosis and congestive heart disease associated with pulmonary infarction are outstanding examples Hemoptysis of cardiac origin is more apt to occur at night probably because of the increased pressure in the pulmonary circulation during sleeping hours An infarcted lung may give rise to copious hemorrhages a point to be remembered since the condition may simulate carcinoma

Blood dyscrasias and vitaminic deficiencies which cause alterations in either the constituents of the blood or the structure of the vessel walls are rare causes of bloodspitting Obvious conditions causing hemorrhage such as foreign body and chest trauma need only be mentioned So called hemoptysis of unknown origin is often due to tracheobronchial varices dry bronchiectasis new growths or nonspecific granulation tissue The differential diagnosis may be established by bronchoscopic examination It is noteworthy that shock or severe chest pain seldom accompanies hemoptysis of pulmonary origin alone If shock occurs it is usually associated with a vascular crisis a condition most often encountered in infarction

Chest Pain

Pain is a dramatic but not a significant diagnostic symptom of pulmonary disease One of the salutary effects of pain in the chest is to cause the patient to seek medical attention This explains partly the comparatively good prognosis of patients with pulmonary tuberculosis and several other diseases which begin with pleurisy This also holds true to some extent for hemoptysis Chest pain is often lacking in advanced lung disease and may be quite severe in the presence of limited involvement An explanation for this seeming paradox is found in the fact that the lungs and visceral reflections of the pleura possess no pain fibers The parietal pleura on the other hand is exquisitely sensitive According to Capps painful areas are concentrated chiefly over the lateral and ventral portions of the pleura and to a lesser degree over the dorsal aspect

Irritation of the central or tendinous part of the diaphragmatic pleura often gives rise to referred pain in the neck the site of origin of the phrenic nerve which has both motor and sensory fibers Irritation of the costal portion of the diaphragm may give rise to pain not only in the lower thorax but also in the abdomen and lumbar regions corresponding to the distribution of the lower six intercostal nerves which supply branches to the periphery of the diaphragm The exact mechanism in the production of pleural pain is not clear Some believe that the pain is due to friction of inflammed pleural surfaces since relief occasionally follows an effusion Some years ago when pneumonthorax treatment of lobar pneumonia was on trial it was noted that separation of the pleural surfaces by air inflation in the cavity brought about marked relief in painful pneumonia Others believe that the pain is caused by hyperalgesia and contraction of the intercostal muscles Still others claim that the pain is due to tension or stretching of inflamed parietal pleura

The sharp sticky pain aggravated on breathing which causes the patient to splint the affected side of the chest is a frequent occurrence in pleuritis of whatever origin As a rule neither the severity nor the distribution of the pain gives an inkling of the nature or extent of the pleural or pulmonary involvement Chest pain is encountered in spontaneously fractured ribs Such stress fractures unassociated with demonstrable pulmonary disease or abnormality of ribs are not rare although they often remain undetected The resulting area of callous formation in the affected rib may be mistaken for intrapulmonary disease Intercostal neuralgia and herpes zoster are also frequent causes of pain In herpes zoster the pain may precede the appearance of skin



Figure 71 Carcinoma of lung masquerading as bursitis A (*Left*) Diffuse ill defined infiltration in left apex (Onset with pain in left shoulder treated with radiotherapy for suspected bursitis) B (*Right*) Six months later circumscribed homogeneous density in left upper lobe (Marked digital clubbing exploratory thoracotomy revealed a carcinoma firmly adherent to apex of chest wall and mediastinal structures nonresectable)

blisters for a number of weeks during which time a neoplasm may be suspected

Pain in the upper chest may be caused by a carcinoma of the so called Pancoast type or by pressure of a cervical rib on the brachial plexus or by an hypertrophied scalenus muscle pressing on the plexus or by involvement of the phrenic nerve anywhere along its course Rheumatoid arthritis or bursitis of the shoulder joint is a frequent cause of pain in the apical region It might be mentioned that rheumatoid arthritis regardless where located may be an early manifestation of carcinoma of the lung (Figure 71) Rose and Ederken described seven cases of nodular nontoxic goiter occurring in association with thoracic pain of a variable pattern Evidence of coexistent myocardial disease was present in two cases In six of the seven cases the goiter was partially or entirely *intrathoracic* Following subtotal thyroidectomy the original thoracic pain either disappeared or was materially modified in all the patients

Chest pain may be the result of cardiocirculatory disease (pericarditis coronary artery disease aneurysm and aortitis) as well as of abdominal disease (subdiaphragmatic abscess disease of the liver gallbladder or gastrointestinal tract) The character of the pain its location its relation to the respiratory cycle the presence of painful sensation along intercostal nerves and the presence or absence of fever must all be taken into consideration As mentioned the time relationship between the appearance of chest pain and cough is occasionally revealing If pain unassociated with other symptoms precedes the cough by an appreciable interval it suggests disease originating in the chest wall rib or intercostal tissues If the pain follows cough it is more likely that the disease is primary in the lungs

I have seen two instances of pain in the lower chest and upper abdomen in conjunction with so called *periodic disease* a condition to which Reimann has drawn particular attention The pain comes in cycles increasing in severity to a point where the patient may require opiates and gradually subsides During this period the patient may also have fever chills and be quite

ill The pain in the lower chest is usually associated with pain in the upper abdomen and often arthralgias The cause of this recurrent disorder which has a familial tendency is unknown There are no specific means of treatment Pain in the chest is also encountered in, so called, epidemic pleurodynia The condition is usually associated with cough, slight expectoration and upper respiratory symptoms The disease has certain features consistent with an acute viral infection since it occurs in epidemics but the exact cause is unknown

Dyspnea

Labored breathing due to anoxia depends on the severity of the oxygen lack on the momentary body requirements and the adequacy of the compensatory mechanism Dyspnea is usually encountered in advanced stages of bronchopulmonary disease It occurs early in disease only if there is a sudden reduction of lung volume as might follow a massive pleural effusion a spontaneous pneumothorax or an obstruction of a major bronchus In the last mentioned, the narrowing of the air passage has to be considerable before dyspnea results Diseases affecting the terminal units of the lungs or the small divisions of the pulmonary artery, as encountered in miliary tuberculosis and pulmonary arteriolosclerosis, are characterized by rapid, shallow respiration rather than labored breathing Orthopnea is as a rule, not encountered in lung disease unless there is superimposed cardiac failure causing pulmonary congestion A sudden occlusion of a major bronchus or a severe asthmatic seizure are among the few exceptions Individuals with advanced tuberculosis, silicosis and emphysema may be dyspneic at the slightest exertion, yet be fairly comfortable when lying down The appearance of orthopnea strongly points to cardiocirculatory failure A practical etiologic classification of dyspnea is furnished by Burchell (Table 7)

Although cyanosis is usually associated with dyspnea, the latter may be present without cyanosis or be out of proportion to the former Such discrepancies are of some diagnostic significance Emphysematous states associated with an increase in corpuscular and hemoglobin content of the blood readily show cyanosis because of the presence of an abnormal concentration of reduced hemoglobin in the peripheral capillaries (at least 5 gr per 100 cc of blood or 7 per cent oxygen unsaturation) Conditions characterized by arteriosclerosis may reveal extreme degrees of cyanosis and comparatively little dyspnea The most severe forms of cyanosis, unassociated with dyspnea are encountered in congenital heart disease in which a septal defect causes a mixture of arterial and venous blood Variable degrees of cyanosis are met in association with cavernous hemangiomas (see Chapter 11) If there is an insufficient amount of unsaturated hemoglobin in the blood, as might occur in anemia, the dyspnea may be quite severe without there being cyanosis Likewise, diabetes and nephritis are often associated with hyperpnea or dyspnea without cyanosis Lastly, there are conditions such as lymphangitic carcinoma of the lungs in which the mechanical interference with blood oxygenation would ordinarily be associated with cyanosis but in which the latter is neutralized by the marked anemia which may be present

TABLE 7

Etiologic Classification of Dyspnea

1 *Mechanical impairment of ventilation*
   - a Muscular weakness, as from poliomyelitis or myasthenia
   - b Skeletal fixation as from marked chest deformity or spondylitis
   - c Hydrothorax pneumothorax
   - d Ascites
   - e Tracheal obstruction bronchiolar obstruction
2 *Impairment of pulmonary distensibility (elasticity and hysteresis factors)*
   - a Pulmonary congestion
   - b Pulmonary fibrosis
3 *Pulmonary insufficiency (inadequate functioning alveolar tissue)*
   - a Emphysema
   - b Extensive inflammatory disease of the pulmonary parenchyma
4 *Inadequate delivery of oxygen to tissues*
   - a Arterial hypoxemia as from high altitude
   - b Anemia
   - c Cardiac failure
5 *Hyperventilation of central type as from acidosis*
   - a Nephritic
   - b Diabetic
6 *Psychic*

From Burchell *Proc Staff Meet, Mayo Clinic* 27 49 1952

Physical Exploration of the Chest

The following remarks will deal with some practical aspects of the physical exploration of the chest. No attempt will be made to enter into details because in the diagnosis of systemic diseases with pulmonary manifestations, of the type described in these pages, the examination of the chest is characterized by the absence rather than the presence of distinguishing physical signs. By and large, in systemic diseases a careful examination of the patient as a whole is more fruitful than the examination of the chest. The appearance of the facies and skin for stigmata of a systemic disturbance, the palpation of the abdomen for enlargement of liver, spleen, other masses, or fluid, palpation for enlarged peripheral lymph nodes and similar examinations are important features in diagnosis.

Inspection

Observing the patient is a most important part of the physical examination. Too often it is the most neglected part. The medical student in his formative years cannot be taught inspection because it is based on experience. "To see is not enough; the accent lies on observation," a difficult art to cultivate (Wartenberg). The busy practitioner, in his haste to apply the stethescope, neglects to develop this faculty. Yet, what a wealth of information is to be gleaned from simply observing the patient. At a glance one notes the approximate age and physique of the individual, whether the illness appears acute or chronic, painful or painless, whether it is associated with respiratory distress or not. One may be struck by the feverish, restless appearance of the patient with an acute pneumonia. The appearance of the emphysematous individual with barrel shaped chest and labored breathing leaves nothing to be desired in the way of a diagnostic aid. The sallow looking man past middle age with cigarette stains on the fingers and evidence of recent loss of weight complaining of pain in the chest, brings to mind immediately a possible carcinoma. The fetid expectoration, digital clubbing and dyspnea are typical of chronic pulmonary suppuration. It is true that looking at the patient will not reveal the early stages of lung disease but neither will the physical examination.

Palpation

It is said of a famous clinician that he once made a diagnosis of tuberculous meningitis simply by putting his hand under the patient's bedcover and palpating an enlarged epididymis. Knowing the frequency with which tuberculous meningitis complicates urogenital tuberculosis, he immediately suspected a hematogenous disease and associated it with the patient's neurological condition. Many renowned physicians have similar anecdotes to their credit, usually of isolated, "snap shot," diagnoses; the many more mistaken diagnoses are charitably overlooked. In the hands of the average physician, palpation gives little information. This, of course, does not detract from the importance of palpating for enlarged lymph nodes, bulging or pulsating masses, displacements of the trachea or the position of the apex beat. Since the vast majority of pulmonary infarcts originate in the veins of the lower extremities, it is good practice to palpate the blood vessels in these locations. Benson and Zavala draw attention to the importance of palpating for areas of costochondral tenderness which may be a source of unexplained pain in the chest. The condition is believed to be the result of stress or trauma to rib structures which produce an irritation or sensitivity of one or more costochondral junctions. Originally described by Tietze, and often referred to as Tietze's syndrome, the condition is not infrequent.

Percussion

Gross alterations in the physical state of the thorax and its contents may be detected by percussing symmetrical areas of each side. Airless lung tissue of significant amount, or fluid in the pleural cavity decrease the normal resonance of the organ. Hyperresonance, even tympany, may be obtained if there is an increase in the air content of the thoracic cage as in the presence of emphysema, giant cavities or pneumothorax. Particularly informative is the percussion note over the lower borders of the lungs on inspira-

tion and expiration An appreciable increase in the area of resonance as the diaphragm descends on inspiration betokens a well functioning lung and one probably free of gross disease But as mentioned in the preceding chapter the percussion note is much more informative after one has examined the chest x ray

AUSCULTATION

With respect to changes in the character of the breath sounds it should be noted that normal breath sounds may be heard in the presence of diseased lung abnormal breath sounds in the presence of healthy lung The most frequent abnormal auscultatory finding in pulmonary disease is either suppressed or exaggerated vesicular murmur Contrary to a prevalent belief fluid in the pleural cavity easily transmits sounds unless there is obstruction of the main bronchi In the presence of a moderate collection of fluid in the pleural cavity the resulting compression of the lung may cause suppression of the vesicular murmur but the tubular sound from the bronchi may be exaggerated

Bernstein and White found that when the pressure of the pleural effusion is constantly positive through all phases of the respiratory cycle one may obtain bronchophony tubular or amphoric breath sounds and even whispered pectoriloquy The pressure must be sufficient to compress the parenchymal tissue down to bronchi of sufficient size to reduce these auscultatory findings I have noted repeatedly that following pneumonectomy the breath sounds may be heard better on the side where the lung had been removed than on the side with the lung intact probably because the marked deviation of the trachea to the operative side transmits the breath sounds through the organized fibrinous exudates and mediastinal structures which fill the hemithorax on the operative side

Alterations in breath sounds are significant if accompanied by rales especially if the latter are confined to a limited area and persist after cough If the rales disappear after cough for a variable interval they probably originate in bronchi and not in lung tissue Deviation of the trachea distortion and displacement of a large bronchus the size and configuration of the chest the depth of the patient's breathing the position of the patient and many other variables influence the character of the breath sounds As a rule the larger the bronchus from which the rales originate the louder and harsher the sounds

Disease of large bronchi associated with loud rhonchi or wheezing rales may be audible without the aid of the stethescope In a detailed study of noises heard with the unaided ear at a distance from the chest Bean mentions the occurrence of this phenomenon in patients with pneumothorax mediastinal emphysema pneumopericardium pulmonary air embolism heart murmurs and several other conditions According to Greene the bubbling clicking and crunching sounds emanating from the chest in the presence of interstitial emphysema are due to the heart rubbing against emphysematous blebs Other knocking sounds may be due to the same cause but also to the heart striking on the diaphragm immediately over a gas bubble in the splenic flexure of the colon in the presence of a left sided pneumothorax

In conclusion it may be stated that the elicitation of abnormal physical signs in pulmonary diseases especially in conditions in which the lungs participate as part of a systemic disturbance is the exception rather than the rule One may elicit abnormal physical signs which are in no way related to the basic disease In fact they are more apt to be due to intercurrent infection secondary cardiac disease or other incidental causes

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Chapters 12 and 13

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The Chest X-Ray: Anatomical and Technical Considerations

Introduction

SINCE THE DETECTION of pulmonary lesions, especially those occurring in the course of systemic diseases, depends almost exclusively on the chest x-ray findings, it is in order to dilate on this aspect of the problem. The following pages will deal chiefly with normal anatomy and developmental anomalies with special reference to such features which come into consideration in differential diagnosis. The more important technical procedures will be defined briefly. It is beyond the scope of this book to enter into technical details which are adequately covered in standard works on the subject. The chapter to follow will be devoted to the limitation and pitfalls of roentgen diagnosis, a matter of great concern to the clinician and one not sufficiently appreciated by the roentgenologist because of his limited contact with the patient and the specific problem under consideration.

Normal Anatomy and Developmental Anomalies

THORACIC CAGE

The cavity containing the lungs consists of bony and soft structures. The former includes ribs, sternum, clavicles, scapulae, spine and the upper parts of the humerus, the latter includes skin, muscle, breasts and the lower portion of the cervical region. One needs to be familiar with the topographic anatomy of the chest and its contents to be able to differentiate shadows which fall within the "normal" range from those caused by disease (Figure 72).

Ribs

Locating and counting correctly the ribs is an important step in localizing disease. The first rib articulates with the first vertebral body, the lower ribs, between successive bodies. The upper articulations of each vertebral body therefore corresponds to the number of the rib attached to it. The anterior articulation of the first costal cartilage is covered by the sternal end of the clavicle. The angle formed by the manubrium and sternum is the site of articulation of the second rib, a landmark in counting ribs anteriorly. Each interspace is numbered by the rib above. The prominence of the seventh cervical spine facilitates the counting of vertebrae and ribs on the posterior surface of the chest. Because of the downward slope of the spinous processes, each tip of the latter corresponds to the level of the vertebral body beneath it. The downward slope of the ribs, from back to front, makes the level of the tenth rib posteriorly to correspond approximately to the level of the sixth, or even fifth rib, anteriorly.

The physique of the individual and the phase of respiration in which the chest x-ray is taken have considerable bearing on the position of the anatomic landmarks. In the presence of emphysema, the ribs assume a more horizontal position giving rise to a barrel-shaped chest; in pleuropulmonary fibrosis, the ribs are drawn together on the side of the major involvement. Scoliosis of the spine results in asymmetry of the two sides of the chest and dislocation of organs. Pectus excavatum may occasionally be suspected in the postero-anterior film by the dislocation of the heart to the left.

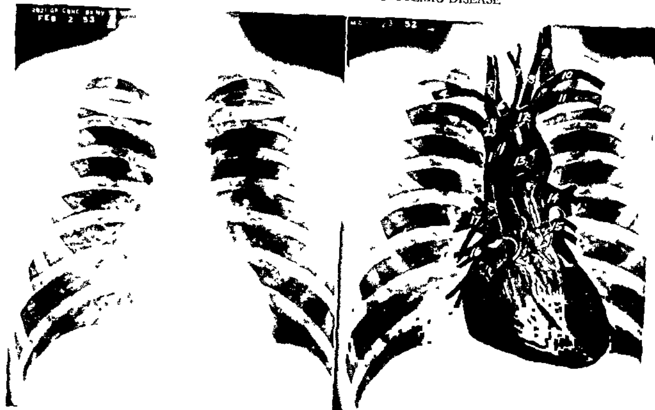


Figure 72. Relation of heart and great vessels to pulmonary structures. A (*Left*) Chest x ray of a healthy adult. B (*Right*) Heart and great vessels superimposed on chest x ray. 1 superior vena cava, 2 right innominate vein, 3 right subclavian vein, 4 right subclavian artery, 5 right internal jugular vein, 6 innominate artery, 7 inferior thyroid veins, 8 left common carotid artery, 9 left internal jugular vein, 10 left subclavian artery, 11 left subclavian vein, 12 left innominate vein, 13 arch aorta, 14 left pulmonary veins, 15 left pulmonary artery, 16 right pulmonary artery, 17 right pulmonary veins.

(Drawn by Jessica Holden after Richard C. Matthias, Department of Visual Education, Baylor University College of Medicine, Houston, Texas.)

Developmental anomalies of ribs are quite frequent. They may be associated with malformation of adjoining vertebrae. The first rib may be rudimentary and abnormally shortened. The anterior portions of the upper ribs may be forked or fused, at times simulating cavity in the lung. An accessory (cervical) rib occasionally articulates with the seventh cervical vertebra on one or both sides. Cervical ribs occur more often on the left side but symptoms are usually more pronounced if they occur on the right side for the reason that most individuals are right handed and there is greater hypertrophy of the attached muscles. In the young, symptoms referable to cervical ribs are rarely encountered. After puberty and completion of rib growth, cervical ribs may cause nervous, vascular or muscular symptoms due to pressure on the subclavian artery or the brachial plexus. It is claimed that the, so called, cervical rib syndrome is more often caused by an unusually wide attachment of the scalenus anticus muscle rather than by the rib itself.

Soft Structures

The folds of skin and muscle projecting in the chest x ray may be a source of misinterpretation. A faint linear shadow produced by a fold of skin is often seen running parallel with the upper border of each clavicle. Giant emphysematous blebs may cause an abnormal degree of translucency of one or both upper lobes. The latter may be seen with the naked eye as soft masses bulging through the anterior triangles of the neck. The same applies to cervical hernias of the lungs, unilateral or bilateral, which may

protrude through the superior aperture of the thorax The site of herniation is between the sternocleidomastoid and scalenus anticus muscles in Sibson s fascia which normally limits the excursion of the pleura and lung

Well developed muscles of the chest, back and neck may interfere with the translucency of the lungs In thin individuals the muscle planes may be distinguishable The sterno mastoid often obscures the apical lung field more so on the side to which the head is turned Large pendulous breasts decrease the illumination of the lower lung fields and may show their margins in the chest x ray, absence of a breast after mastectomy or as a result of underdevelopment causes hyperillumination Darkly pigmented or prominent nipples in thin individuals often project as circular opacities simulating metastatic lesions The superior vena cava and innominate vein form the right border of the superior mediastinum the shadow of the latter often infringing on the inner aspect of the right upper lobe especially if the patient is not centered properly

Diaphragm

This muscle arches in two leaves the dome of each projecting into a corresponding hemithorax at a higher level on the right than on the left The inclusive height of the diaphragm is measured at the level it reaches on the right side near the spine This usually corresponds to the level of the tenth dorsal rib in midrespiration In the lateral projection the anterior portion of each leaf reaches the higher level the posterior portion making a sharp curve downward In obese persons especially one may find a well defined triangular shadow at one or the other costophrenic angles more often the left The shadow has a rather soft density and represents an extrapericardial collection of fat In the lateral projection the density cast by the pad of fat is seen to lie anteriorly adjacent to the sternum Such shadows are often a source of confusion requiring additional diagnostic procedures including a complete gastrointestinal visualization and a barium enema to rule out a parasternal diaphragmatic hernia through the foramen of Morgagni as well as congenital pericardial cysts and diverticula Bronchoscopy and bronchography may also be indicated to rule out carcinoma

The posterior recess of the diaphragm is quite deep and accommodates several hundred cc of fluid an amount insufficient to be detected in a conventional P A chest x ray It should be noted that an infrapulmonary pleural effusion may simulate a high diaphragm Friedman collected seventeen such cases in a relatively short time The induction of a pneumoperitoneum is a useful diagnostic aid if the fluid is on the right side Insufflating the stomach with citrocarbonate or a Seidletz powder will accomplish the same purpose on the left side

The vertebral portion of the diaphragm is of particular interest because this part is pierced by openings through which pass the esophagus, aorta vena cava azygos vein and thoracic duct, as well as the vagus and sympathetic nerves The diaphragmatico esophageal membrane and the loose attachment of the peritoneum constitute a vulnerable site for hiatus hernias Barium examination for diaphragmatic hernia is important in every gastrointestinal examination The symptoms of diaphragmatic hiatus hernia may simulate those of angina pectoris gallbladder disease duodenal ulcer and carcinoma of the terminal esophagus or cardia of the stomach Unexplained anemia and intractable cough may be caused by hiatus hernia The frequent occurrence of a pleural effusion in a costophrenic sinus as part of a systemic disease has been mentioned repeatedly in these pages

Occasionally there is noted a double contour of the right leaf of the diaphragm more evident in the lateral projection The bulge is due to the pushing upward of a mass of liver and may simulate a tumor (Figure 49) Richman and Barry reported four such cases two having been referred with a diagnosis of tumor and one with that of subdiaphragmatic abscess One of the patients was submitted to exploratory thoracotomy before the diagnosis was established However a thoracotomy should rarely be necessary A diagnostic pneumoperitoneum will reveal a layer of air between diaphragm and liver and help clarify the situation Other features in the

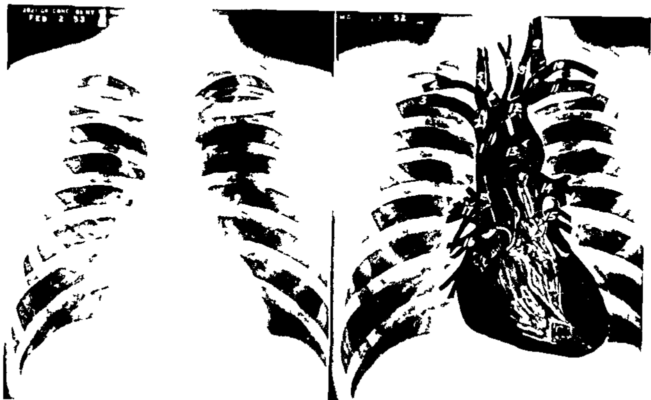


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differential diagnosis of an abnormally elevated diaphragm are discussed in Chapter 10

In the presence of advanced emphysema or pneumothorax, the insertion of the costal components of the diaphragm are sometimes seen as step-like irregularities The latter are brought out best in the inspiratory position An uneven pull of the pericardial ligaments may also produce irregularities of the muscle The diaphragm is often fixed at one or both costal margins by *pleural adhesions with obliteration of the* normally clear costophrenic sinuses

Mediastinum

The mediastinum and its contents cast the central shadow in the chest x ray The space is bounded mesially by sternum, posteriorly, by the spine and below by the diaphragm Prior to the widespread utilization of roentgenography and thoracic surgery, the mediastinum was a relatively unexplored region But with the introduction of methods of precise localization and safe exploration, the mediastinum has assumed considerable importance Nonetheless, a differential diagnosis of disease within the space still presents many difficulties

In the lateral projection, the one necessary for proper delineation of the space, the mediastinum is seen to consist of three compartments in relation to its chief contents the pericardial sac and heart The anterior mediastinum is an illuminated space between the sternum and pericardium and contains the thymus or its remains, and the anteromesial projections of the lungs This space also contains lymph nodes, fat areolar tissue and branches of the internal mammary artery The major abnormalities which may affect the retrosoternal region or the anterior mediastinum are tuberculosis of the chondrosternal and chondrocostal junctions which may give rise to cold abscesses of the chest wall Tumors of the sternum or costal cartilages are rare The anterior mediastinum is also the site of intrathoracic substernal thyroid simple enlargements or neoplasms of the thymus gland including mediastinal lipomas dermoid cysts and teratoid tumors originating in congenital rests Tumors of lymphatic origin including the lymphomas, lymphosarcoma and Hodgkin's disease, as well as cystic tumors, are also *most often* found in the anterior mediastinum

The middle mediastinum, the dense portion of the space, contains the heart and the point of origin of the great blood vessels The phrenic nerves run through this space The more important abnormalities affecting the middle mediastinum are obviously those associated with diseases of the heart and major blood vessels

The posterior mediastinum, an illuminated space between the heart and spine, contains the trachea and main bronchi, esophagus the thoracic portion of the descending aorta, azygos and hemiazygos veins, thoracic duct, vagi sympathetic and splanchnic nerves Bronchiogenic cysts are found at points of bifurcation of the trachea and major bronchi The tracheobronchial lymph nodes occupy the angles between the trachea and each bronchus the bronchopulmonary lymph nodes are found at the root of each lung These structures are often the site of metastatic disease This region is the favored site of neurogenic tumors originating in spinal intercostal or sympathetic nerves

The region immediately above the aforementioned three compartments is the superior mediastinum Anatomically, the latter lies between the manubrium sterni anteriorly and the upper four thoracic vertebrae posteriorly But inasmuch as the major structures occupying this region continue into the posterior mediastinum, the superior and posterior divisions are, for practical purposes, considered as one The superior mediastinum contains the aortic arch and great vessels, the innominate veins and superior vena cava, trachea, esophagus, thoracic duct, thymus as well as the phrenic, vagi and left recurrent nerves As mentioned, the superior mediastinum is a frequent site of suppuration originating in the throat, spine and esophagus

Superior Vena Caval Obstruction

Obstruction of the superior vena cava may be found in association with malignant lymphomas metastatic carcinoma and other systemic diseases The major causes of caval obstruction are aortic aneurysms, bronchogenic carcinoma

with mediastinal involvement and thrombosis (Figure 73) In 1934 Ehrlich and co workers reviewed the literature and compiled 309 reported cases In 1949 Hinshaw collected an additional 127 cases The obstruction may be complete or incomplete The location and extent of the collateral circulation depends upon the site duration and completeness of the obstruction Katz and co workers found by means of phlebography with diodrast that if the site of occlusion of the superior vena cava is above the point of entrance of the azygos vein the latter and its tributaries are the main collateral channels and therefore visible collateral circulation is not extensive A few dilated veins may be seen in the neck shoulder regions and upper part of the chest If the obstruction is below the azygos vein an extensive collateral circulation is visible in the chest back groin and abdominal wall representing anastomosis between the superior and inferior vena caval system

Obstruction of the superior vena cava below the entrance of the azygos vein is tolerated with much more difficulty because the blood has to take a circuitous route by way of the inferior vena cava to reach the heart Additional diagnostic criteria of obstruction of the superior vena cava are the demonstration of significantly elevated venous pressure (180 mm water or above) in the upper half of the body in the presence of normal venous pressure in the lower half and the demonstration of a collateral circulation over the upper half of the body chiefly the front of the chest The collateral circulation may be outlined by infrared photography and better still by phlebography By means of the latter it is possible to demonstrate the point of obstruction or the presence of a mass or other lesion

HILUS

The hilus is not a distinct space rather an eccentric wedge shaped depression in the mesial surface of each lung Through the hilus pass the various structures which make up the root of the lung Although it is difficult to define what constitutes a normal hilus distinctly pathologic states are usually evident if one makes due allowance for the age occupation and previous lung infections of the individual The main hilar shadow is composed almost exclusively of the pulmonary artery and its major subdivisions and to a lesser degree veins Normal bronchi do not cast shadows in the chest x ray, nor does the latter reveal densities cast by bronchopulmonary lymph nodes unless they are involved in a diffuse lymphangitic process Occasionally one sees adjacent to the hilus one or more oval translucent areas cast by cross sections of large bronchi Adjacent to these one may find similar densities representing blood vessels caught on end

The important structures of the hilar region exclusive of the large blood vessels are the lymph nodes which drain the lungs and pleura Systemic diseases notably the malignant lymphomas and sarcoidosis as well as generalized lymphohematogenous infections sooner or later involve the bronchopulmonary tracheobronchial and paratracheal lymph nodes The structures entering the hilus of each lung occupy the middle mediastinal space Since the major occupant is the heart in the pericardial sac large neoplasms primary as well as metastatic involving this region are displaced anteriorly posteriorly or superiorly The contents of these mediastinal spaces are visualized in lateral chest x ray projections With the marked increase in the use of chest roentgenography and the recent advances in thoracic surgery these several compartments of the mediastinum have assumed tremendous importance What was once unexplored No Man s Land is now Main Street

LUNGS AND FISSURES

The lungs lie freely in the pleural cavities attached only at the root and by the pulmonary ligaments Each organ is conical in shape assuming the configuration of the cage in which it is confined The right lung is slightly larger shorter and wider than the left due to the greater bulk of the right lobe of the liver and the left sidedness of the heart The volume ratio of the right lung as compared to the left is approximately 55 45 The lungs are marked by surface impressions corresponding to the position of the ribs heart and large blood vessels Each organ has an apex base three surfaces and two margins The right lung has two fissures which divide the org



(*See legend on opposite page.*) →

three lobes The left lung has one fissure dividing the organ into two lobes Quite often the horizontal fissure dividing the upper and middle lobes is either incomplete or absent an important consideration in the surgical treatment of disease The parenchyma of the lung is characterized roentgenologically by a delicate webbing composed chiefly of vascular elements The striations are densest in the inner and lower lung fields The translucency of the organs varies in its vertical plane i e from hilus outward Moderate emphysema accentuates the vascular markings advanced emphysema obliterates them

Developmental Anomalies

There may be a congenital absence (aplasia) of a lung (Figure 74 A) or varying degrees of defective development (hypoplasia) The roentgen features which distinguish these conditions from acquired disease are found in the frequent coexistence of structural defects of the trachea bronchi and blood vessels the symmetry of the thoracic cage and the absence of hypertrophy of the right side of the heart In 1950 Ingram and co workers collected from the literature the reports of fifty five proved cases of aplasia of the lung including sixteen in which the diagnosis was made during life These investigators reported two additional cases of aplasia of the lung diagnosed during life In one a corroborative angiocardiographic examination revealed a single pulmonary artery They noted that the condition is usually asymptomatic and discovered accidentally It occurs more frequently in males and three times as often on the left side as on the right

Situs Inversus and Bronchiectasis (Kartagener s Syndrome) In recent years the elements of bronchial obstruction and infection have been rightly endowed with much greater importance in the development of bronchiectasis than the possible factor of a congenital weakness of the respiratory tract In occasional cases however bronchiectasis may be due to failure of bronchiolar canalization during embryogenesis causing arrested development of corresponding bronchopulmonary segments Instances of situs inversus and bronchiectasis lend support to this belief Although the association of complete transposition of the viscera with bronchiectasis was noted previously Kartagener in 1933 was the first to point out the greater frequency of bronchiectasis with sinusitis in persons with situs inversus Situs inversus occurs in approximately 1 in 8 000 persons bronchiectasis in about 20 per cent of persons with situs inversus

Kartagener s syndrome is an inherited anomaly and is often associated with developmental defects of other parts of the body Olsen found that eleven of eighty five patients with situs inversus had congenital anomalies of the heart hydrocephalus imperforate anus cleft palate flail thumb and accessory digits Other investigators have also noted a high incidence of congenital malformations in association with Kartagener s syndrome The vast majority of patients with this condition are discovered in infancy Bergstrom and co workers reported a family in which there occurred among six siblings two cases of transposition of viscera sinusitis and bronchiectasis as well as other anomalies and two of bronchiectasis without situs inversus These authors tabulated the reports of eighty cases of Kartagener s syndrome previously reported The following is a classical example

Case 32 Male—Age 22

The patient was admitted to the Morrisania City Hospital with fever chills and productive cough The story was that he had been treated since youth for sinusitis repeated seizures of bronchitis and bronchopneumonia On a previous admission to the Morrisania City Hospital the patient was found to have situs inverus Of interest in the family history was the fact that the patient s father who had died

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Figure 73 Superior vena caval obstruction A (*Upper left*) Marked swelling of face neck and chest engorgement of blood vessels of upper chest and shoulder B (*Upper right*) Considerable widening of superior mediastinum rounded masses extending into adjacent lungs scattered infiltrations in right upper lobe C (*Lower left*) After radiotherapy marked reduction in swelling of face and neck vascular pattern less prominent D (*Lower right*) Considerable decrease in superior mediastinal density (Biopsy of lymph node revealed malignant lymphoma)



Figure 74 Developmental bronchopulmonary anomalies A (*Left*) Homogeneous density obscuring entire left hemithorax heart and mediastinum displaced to the left (Agenesis of left lung in an infant also cervical spina bifida on bronchoscopy only the left main bronchus was visualized bronchography failed to reveal iodized oil in the left bronchial tree) B (*Right*) Delicate line extending to the *apical pleura from a bulbous end at the* upper mediastinum giving appearance of an inverted comma (Azygos lobe in a child)

of tuberculosis four years previously also had dextrocardia

The physical chest x ray and laboratory findings revealed a pneumonia in the right upper lobe In addition the chest x ray showed a complete dextrocardia (Figure 75A) The frontal sinuses were rudimentary The ethmoids and maxillary sinuses showed marked opacification suggestive of exudate Bronchography revealed extensive dilatation of the bronchi in both lower lobes more marked on the left side (Figure 75B) The patient responded to antibacterial treatment and was discharged to the Chest Clinic with the plan that when the infection cleared completely it might be feasible on some future date to treat the patient s bronchiectasis surgically

Azygos Lobe A fairly frequent developmental anomaly is the finding of a split upper lobe The malformation is due to an abnormal position of the azygos vein during its embryologic development Instead of entering the superior vena cava posteriorly at the hilus the azygos vein runs laterally arches over and bisects the upper lobe The septum dividing the lobe consists of two layers of parietal pleura and two layers of visceral pleura since the azygos vein lies extrapleurally The vein lies at the base of the septum The roentgen appearance of the azygos lobe is featured by the presence at its lower margin of a thin delicately curved line extending *from the chest wall to the upper mediastinum* The line ends in a rounded density mesially the site of the azygos vein The appearance of the line is likened to that of an inverted comma (Figure 74B)

Ellis and Bruwer noted that on occasion the azygos vein may cast a shadow in the chest x ray which may be misinterpreted as a mediastinal tumor Several instances are cited where exploratory thoracotomy had been carried out in which a mediastinal shadow was actually due to a dilated azygos vein Cases are also on record of pneumonia and tuberculosis limited to the azygos lobe Enlargement of the density cast by the azygos vein may be noted in cases of su

perior vena caval obstruction inferior vena caval obstruction portal hypertension and heart failure

Inferior Accessory Lobes One may encounter inferior accessory lobes which appear as areas of increased density or illumination depending on the state of the parenchyma Rigler and Ericksen quote Schaffner who found at postmortem examination partially or entirely formed inferior accessory lobes in no less than 45 7 per cent of 210 human lungs In the chest x ray the interlobar septum demarcating an inferior accessory lobe is seen as a fine linear shadow extending from the medial portion of the diaphragm upward and mesially toward the hilum The diaphragm may show a triangular dimpling at the point of origin of the fissure

Bronchovascular Anomalies Of current interest is the occasional finding of a so called intralobar sequestration of the lung Pryce and coworkers described eight examples and Wyman and Eyler reported seven additional surgically and pathologically proved cases Isolated case reports have been published by others It would seem that intrapulmonary sequestration is not rare and will probably be encountered more often once the condition is better recognized

Intralobar sequestration is associated with one or more abnormal arteries arising from the lower thoracic or upper abdominal aorta or some other vessel Such anomalous arteries have the same histological structure as the aorta containing a relatively large amount of elastic tissue and being subject to atheromatous changes due to systemic pressure variations Anomalous arteries carrying oxygenated blood from the aorta may enter normally placed lung tissue in which case they are more commonly encountered on the right side and may be bilateral The most common site of origin of anomalous pulmonary arteries is from the descending aorta above the level of the diaphragm and in relation to the inferior pulmonary ligament

The ectopic mass of lung tissue does not usually connect with the bronchial tree but is attached to a blind bronchus In case of the latter the sequestered mass is devoid of carbon pigment The sequestered portion of lung may be composed of normal tissue or may be bronchiectatic or cystic The mass may lie within the

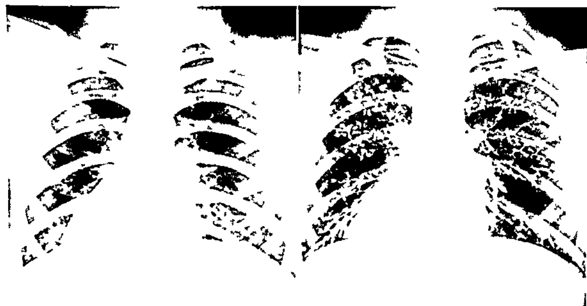


Figure 75 *Case 32* Situs inversus and bronchiectasis (Kartagener s syndrome) A (*Left*) Dextrocardia soft infiltrat on in right upper lobe B (*Right*) Bronchogram shows extensive bronchiectasis, more marked on left air containing stomach is seen faintly beneath right leaf of diaphragm (X rays showed rudimentary frontal s nuses and opacificat on of ethmoids and maxillary s nuses)

lower lober or adjacent to the left lower lobe At times, the sequestered lobe or lung may appear as a giant cyst Accessory lobes, in contra distinction to intralobar sequestrations, are entirely separate from the parent mass and the supplying pulmonary artery and veins arise normally from the hilus Lower accessory lobes are sometimes referred to as extralobar sequestrations A congenital diaphragmatic hernia may coexist Almost invariably extralobar sequestrations are found on the left side, the intralobar form may be found on either side

Bronchovascular anomalies are discovered accidentally or as a result of symptoms due to secondary infection Infection is common in intralobar sequestration, the condition often appearing as pulmonary abscess, empyema, subdiaphragmatic hernia or bronchiectasis It is important to be aware of the existence of intralobar sequestrations because in the resection of such masses, the surgeon has to be on guard lest he cut the artery or arteries communicating with the aorta A number of deaths have been reported as a result of such accidents

I have had under my observation three patients with intralobar sequestrations A man of 27 was found to have a large, oval, circumscribed density showing several fluid levels in the region of the left lower lober behind the heart A cyst was suspected, but at operation, performed by Dr Morris Rubin an intralobar sequestration was discovered attached to a large artery which had pierced the diaphragm The mass was excised successfully The second patient, a girl of sixteen, was found to have a somewhat smaller rounded density at the right cardiophragmatic angle In this case, an intralobar sequestration was suspected prior to the operation and the surgeon warned that he might encounter an anomalous blood supply This proved to be the case At operation an aberrant artery was found originating above the level of the diaphragm The mass was resected successfully and the patient made an uneventful recovery Because of several unusual features associated with the following patient, a brief history of the case is worth citing

Case 33 Male—Age 27

The patient became ill in 1931, at the age of nine years *He was admitted to a hospital in North Carolina and had a left-sided thoracotomy* and rib resection for a presumed empyema A draining sinus remained but the patient had no respiratory difficulties and was able to work at heavy manual labor The patient cleansed and dressed the thoracotomy wound and reinserted the drainage tube when necessary In 1940, the patient came to New York City and entered a city hospital with the hope of having the draining sinus eradicated At this time the disease in the chest was ascribed to 'an old draining abscess of the left lower lobe, but the possibility of an encapsulated hydropneumothorax could not be excluded" A thoracoplasty was done and the 7th, 8th 9th and 10th ribs resected A year later the patient reentered the same hospital for a revision thoracoplasty and in 1945 he returned for a third time and an additional attempt was made to obliterate the presumed empyema space with a Schede thoracoplasty However, the patient was left with a large wall defect He went back to work in a factory, caring for the wound himself

When I saw the patient, in May, 1950, he had slight unproductive cough but otherwise few symptoms referable to the chest Examination revealed an underweight Negro male with cyanosis and clubbing of the fingers and toes There was a large defect in the left lateral chest wall measuring 7 x 7 centimeters (Figure 76C) The surrounding skin was extensively scarred as a result of previous operations The interior of the defect showed the presence of a glistening membrane with numerous ridges and trabeculations The membrane was very flexible and herniated through the chest opening on deep cough At the apex of the space, there was a small opening which appeared to communicate with a bronchus The remainder of the physical examination was noncontributory The chest x ray revealed extensive loss of bony thorax over the left lower chest due to previous thoracoplastic operations The upper lobe was partly aerated The right lung was clear, the heart displaced to the right (Figure 76A)

The patient was admitted to the Morrisania City Hospital on May 8, 1950 A congenital cyst of the lung was suspected and operation advised At operation performed by Dr Morris Rubin the left lung was found attached to the periphery of the large defect previously described The defect was incised along its circumference to permit detach

ment from the chest wall The muscle layers were then opened along the line of incision and a long segment of the lowest intact rib (5th) resected subperiosteally and the pleural cavity opened The upper lobe was found to be free of adhesions The lower lobe was completely replaced by a huge solitary lung cyst which had been marsupialized The entire lung was mobilized by the separation of the lung cyst from its thoracic attachments

A pneumonectomy was done by individual ligation of the pulmonary artery superior and inferior pulmonary veins The bronchus was isolated clamped and cut and the stump closed with a single row of 0000 silk The stump was then covered with adjacent pleura *Two aberrant arteries were found originating from the thoracic aorta entering the cyst wall* Both of these vessels were ligated and cut (Figure 76F)

In order to close the chest wall defect a thoracoplasty was performed including segments of the 2nd 3rd and 4th ribs Part of the 2nd rib was left intact due to a congenital fusion with the 1st rib also because the patient s blood pressure had dropped The soft tissues of the chest wall were then mobilized posteriorly to the dorsal spine and anteriorly to the sternum It was possible to close the decostalized thoracic cage except for a small defect

The postoperative course was uneventful except for an elevated temperature associated with a breakdown of the wound at the area of the previous operations At that site there was necrosis of the skin which subsequently sloughed leaving a small opening A draining sinus persisted for about three weeks and healed spontaneously Sutures were removed during the second week postoperatively and the remainder of the wound healed by primary union in spite of the poor blood supply and tension at the suture line The patient did well and was discharged At first he noted dyspnea on exertion but it gradually disappeared (Figures 76B and D)

Interlobar Fissures

In considering the topographic anatomy of the fissures, a distinction needs to be made between the cadaveric and roentgen positions Furthermore one has to take into consideration the fact that the chest x ray exposure is customarily made in inspiration Lachman has drawn attention to the fact that the landmarks acquired at the dissection table are not necessarily applicable to the chest x ray He points out, for example, that the bifurcation of the trachea is generally placed at the level of the intervertebral disc between the fourth and fifth thoracic vertebra, but in the chest x ray taken in the upright position the bifurcation is considerably lower and undergoes shift with the respiratory cycle

Brock has also drawn attention to the fact that the surface projections of the positions of the main interlobar fissures, as generally taught, are inaccurate being given at a higher level than is actually the case The right main fissure ends at the costal pleura at least 4 cm lower, or corresponding to the fifth rib near the vertebral column rather than to the level of the third thoracic spine and the fourth rib The fissure follows the fifth rib until its costochondral junction and then slopes downward to the sixth rib The interlobar fissure of the left lung leaves the vertebral column at a less definite point ranging from the level of the third to the fifth ribs sloping more vertically downward to reach the level of the seventh rib anteriorly

Because of the obliquity of the main fissures and resulting overlapping of lobes it is obvious that only lateral projections of the thorax can show their slope provided, of course, the fissures are discernible The fissures are important structures not only because they form the boundaries of lobes but because they are potential spaces for fluid The appearance of the lung margins at the fissure junctions may give a clue as to the state of the corticopleural layer of the organ as a whole

The main interlobar fissure of each lung extends obliquely downward and forward from the front of the vertebral column to the sternum The main fissure of the right lung gives off a secondary horizontal fissure in the posterior axillary line which runs anteriorly and slightly upward separating the upper from the middle lobes The position of the horizontal fissure can be marked by a line drawn from the posterior axilla at the level of the fifth rib or interspace to the fourth costal cartilage In the conventional postero anterior view the horizontal fissure is often found at the level of the third and as low as the fifth costal cartilages



Figure 76 *(See legend on opposite page)*

Figure 76 Case 33 Bronchovascular anomaly intralobar sequestration in form of a giant cyst simulating emphysema A (*Opposite page upper left*) Extensive loss of bony thorax of left [illegible] chest [illegible] er [illegible]

[illegible] of thoracoplasty) C (*Opposite page lower left*) Large ovoid defect of chest wall (interior of defect showed glistening membrane with numerous ridges) extensive scarring of skin from previous operations D (*Opposite page, lower right*) Appearance of chest wall after operation closure of defect E Large solitary cyst showing many trabeculations



The right middle lobe is not in contact with the posterior chest wall For practical purposes therefore physical findings elicited over the back of the chest from the base to the midscapular level may be assumed to originate in the lower lobe, above it in the upper lobe All the lobes excepting the right upper are in contact with the diaphragm As a result disease of any lobe excepting the right upper, may cause pain not only in the chest but also in the abdomen The anterior portion of the right horizontal fissure separating the right upper and middle lobes is often seen in the posterior anterior projection since the plane of the fissure is tangential to the central ray The fissure here is usually at the level of the fourth rib Because of the slight angulation of the fissure the posterior anterior view may show a parallel line below the fissure

Terminal Lung Radicles

The air spaces through which gas exchange takes place make their appearance as small projections in the terminal respiratory bronchioli (Miller) The latter correspond to the ultimate subdivisions of the pulmonary artery which form vascular ducts about each lobule Each primary lobule consists of a duct which leads by a number of atria to sacs the lining of which is composed of alveolar epithelium The distal end of each alveolar duct is surrounded by a sphincter composed of muscle bands Intercommunications have been shown to exist between al

individual lobes allowing collateral circulation of air and fluid These interalveolar pores play an important role in the spread of disease

Many of the diseases described in these pages involve primarily or chiefly the terminal radicles of the lungs This applies not only to blood borne diseases or disease of the vascular system but also to pulmonary lesions associated with metabolic, hyperergic, hematologic and other disorders The symptoms of anoxia, often encountered in these systemic diseases are frequently caused by an alveolar-capillary block interfering with the transfer of oxygen through thickened alveolar membranes

Bronchi and Bronchopulmonary Segments

The main bronchi arise in the trachea at the level of the fourth or fifth dorsal vertebrae, corresponding anteriorly to the second or third costal cartilages The point of division, the carina is a prominent ridge formed by fusion of tracheal and bronchial cartilages Each main bronchus and its subdivisions permeate the lung in a tree like manner The musculature of the bronchi consists of spiral and circular fibers which allow a rhythmic elongation and widening on inspiration and contraction on expiration The bronchial cartilages disappear at the bronchioli, the latter being circular tubes composed of smooth muscle bands

The right main bronchus, except for a slight lateral deviation of about 25°, is almost a direct continuation of the trachea This anatomic continuity explains the predilection of the right lower lobe to aspiration pneumonia and foreign body lodgement Possibly, too, the fact that most individuals are inclined to sleep on the right side is also a factor The right main bronchus extends for a short distance from the carina and gives rise at an angle of about 90° to an upper bronchus supplying the right upper lobe The main channel (intermediate bronchus) continues to a lower level at which point it gives off secondary divisions, at approximately the same level, to supply the middle and lower lobes The left main bronchus gives off first one branch to the left upper lobe which immediately divides itself into two, one supplying the upper division of the left upper lobe and the other, the lingula A second major branch supplies the left lower lobe

Inasmuch as many pathologic processes affect initially segments rather than complete lobes each of the latter is recognized as a composite of bronchopulmonary segments A bronchopulmonary segment is an area of lung supplied by a relatively constantly placed bronchus, the orifice of which is situated in a large lobar bronchus and is visible to the bronchoscopist (Kramer and Glass) In localizing disease, the surgeon is particularly concerned with the segmental distribution of the bronchi and the projection of the latter on the surface of the chest A number of attempts have been made to establish a bronchial nomenclature which can be used by bronchoscopists, roentgenologists internists and surgeons

The classification devised by Jackson and Huber, based on bronchoscopic and anatomic studies, has been accepted as the official nomenclature by a number of interested specialty groups The principle arteries on each side are identified with the same nomenclature as that used for the bronchial segments The bronchopulmonary segments cannot be considered as morphologic bronchovascular units because of the frequency with which blood vessels traverse one segment to the other Table 8 gives the nomenclature of the bronchial tree and corresponding bronchopulmonary segments, according to the Jackson-Huber classification (Figure 77)

TABLE 8

Nomenclature of the Bronchial Tree and Corresponding Bronchopulmonary Segments

Right Lung			Left Lung		
Lobes	No	Segments	Lobes	No	Segments
Upper	1 2 3	Apical Posterior Anterior	Upper Upper division	11 12	Apical posterior Anterior
Middle	4 5	Lateral Medial	Lower (lingular division)	13 14	Superior Inferior
Lower	6 7 8 9 10	Superior Medial basal Anterior basal Lateral basal Posterior basal	Lower	15 16 17 18	Superior Anteromedial basal Lateral basal Posterior basal

From Jackson and Huber *Dis Chest* 9 319 1943

The right middle lobe, lingula and the superior, also the basal segments of the lower lobes

merit additional comment because involvement of these parts often presents problems in diagnosis. To a considerable degree the difficulties lie in lack of precise knowledge of the roentgenologic anatomy of these segments.

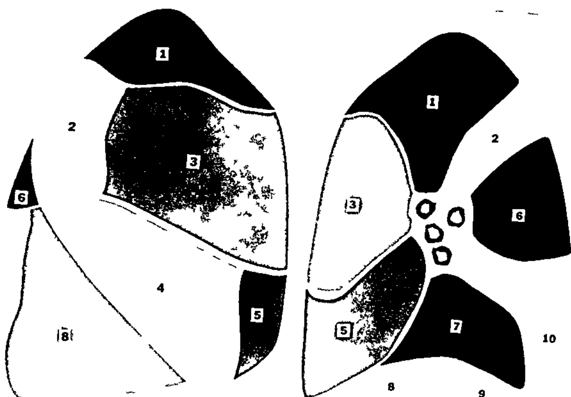
Right Middle Lobe

This lobe is separated from the right upper lobe by a horizontal fissure and from the lower lobe by an oblique fissure. Laterally the middle lobe is in contact with the lower anterior aspect of the chest, medially with the right side of the heart and posteriorly with the lower lobe. The costal portion of the lobe is triangular, the cardiac portion quadrilateral. In more than 50 per cent of cases the horizontal fissure is incomplete or absent with the result that in these the middle lobe is either partially or completely fused with the upper lobe. Because of the obliquity of the main fissure and the fact that the middle lobe lies anteriorly to the lower lobe, roentgenologic study requires lateral as well as postero-anterior positioning of the patient. A postero-anterior projection does not suffice for the additional reason that if the middle lobe is shrunken it retracts to the hilus and its place is filled with overdistended lung. Although the lateral projection is obviously more revealing, the contracted lobe may be obscured by densities cast by the heart and hilar structures. For these reasons an exact delineation of middle lobe disease often proves difficult.

The right middle lobe is composed of two bronchopulmonary segments, one situated laterally, the other medially. Either or both segments may be involved. Obstruction of the lateral (costal) division of the middle lobe bronchus is characterized in the P A projection by a diffuse cloudiness extending into the lower lung field, a relatively clear zone separating the density from the right border of the heart. In the lateral projection the density appears triangular and is situated low and posteriorly. Obstruction of the medial (cardiac) division of the middle lobe bronchus produces in the P A projection an irregular density immediately adjacent to the right border of the heart. In the lateral projection the density appears quadrilateral lying immediately behind the sternum and beneath the horizontal fissure.

In addition to the postero-anterior and lateral projections, supplementary procedures are often necessary, the most important being a lordotic view, tomographs and bronchographs (Figure 78). The last mentioned is best combined with bronchoscopy because the diagnosis usually has to take into consideration a possible neoplasm especially in older age groups. The most frequent cause of contraction often associated with bronchiectasis of the middle lobe is a constricting collar of lymph nodes about the orifice of the right middle lobe bronchus. The roentgenographic appearance of a shrunken middle lobe or the right middle lobe syndrome may be simulated by interlobar pleurisy or pleuropericardial adhesions. A triangular density formed by the superimposed lower cardiac border and an elevated right leaf of the diaphragm and even a contracted, depressed anterior segment of the right upper lobe may also simulate right middle lobe disease.

The vulnerability of the right middle lobe to cicatricial contraction of lymph nodes may be explained on anatomical grounds. Nelson, Brock and others have shown that the bronchus to the right middle lobe more so than the bronchus to any other lobe is subject to compression by enlarged lymph nodes which may cause atelectasis of the lobe. These investigators draw attention to the fact that the right middle lobe bronchus as it leaves the main channel forms an acute angle. At the point of bifurcation the bronchus is surrounded by a chain of lymph nodes which drain the lymphatics not only of the middle lobe but also of the lower lobe. When these bronchopulmonary lymph nodes become enlarged, they are apt to exert pressure on the middle lobe bronchus. Should the bronchial channel become obstructed the lobe collapses, leading in many instances to bronchiectasis. Bronchiectasis has been observed repeatedly in children who have gone through the primary infection with the tubercle bacillus, especially in those who had signs of bronchial compression. In addition to shrinkage and bronchiectasis the middle lobe may be the seat of pneumonia, suppuration or neoplasm.



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(*See legend on opposite page*)

Adler and co workers reported three cases of middle lobe disease due to histoplasmosis and one, to sarcoidosis

Lingula of the Left Upper Lobe

A counterpart of the right middle lobe is the lingula or the lower division of the left upper lobe. In a study of cleft upper lobes Boyden found that 8 per cent of left lungs exhibited a 'middle lobe' in various degrees of separation ranging from a 'true middle' or lingular lobe to an ectopic arterial type. In health the lingula lies anteromedially, adjacent to left border of the heart. It is roughly triangular in shape, the borders not well delineated. The lingula is supplied by the first branch of the left upper lobe bronchus and bifurcates into superior and inferior divisions. A diseased lingula may occasionally be seen in overexposed films as a dense mass behind the cardiac silhouette. Its exact definition requires left lateral projections, bronchography and the other procedures mentioned previously (Figure 79).

Superior Segments of Lower Lobes

From the nature of their embryologic development, bronchial distribution and blood supply the lower lobes appear to be made up of two distinct parts. Each has two secondary bronchi, one supplying the superior and posterior portion of each lobe, the other the basal portions. Occasionally the superior segment is separated by a well defined fissure. Disease limited to a superior bronchopulmonary segment of a lower lobe is projected in the hilar region in the P A chest x ray. On the other hand disease affecting a basal bronchopulmonary segment is projected into a costophrenic sinus simulating a pleural effusion. Practically the entire superior segment lies behind the upper lobe of each lung. The basal segments lie below the shadow of the diaphragm. In the P A chest x-ray, therefore, only a small portion of the lower lobe is projected.

The status of a superior segment of a lower lobe is of prime importance in the treatment of disease, especially tuberculosis, for the reason that the superior segment is often involved in association with disease of an upper lobe or of the middle lobe. Tomography in the lateral as well as in the postero anterior projections are necessary to determine the condition of the superior segment of the lower lobe before resectional surgery is done. In addition to tuberculosis the superior segments are vulnerable to carcinoma and aspiration infections, including lung abscess.

Basal Segments of Lower Lobes

The major departure in the distribution of the basal segments of the right and left lower lobes is the combined anterior and medial segments of the left lower lobe into a single unit. In the postero anterior projection only the lowermost tips of the anterior basal segments are visible at the costodiaphragmatic sinuses. Collapse of the right lower lobe is particularly frequent because the supplying bronchus is in almost direct continuity with the main channel and, as a result, foreign bodies and aspiration infections are apt to gravitate to that side.

Although the major roentgen features of a collapsed lower lobe are similar on both sides there are a few points of difference. Collapse of the right lower lobe often involves also the middle lobe because the origin of the two lobar bronchi are at approximately the same level. The fact that the atelectatic left lower lobe recedes behind the cardiac shadow prevents its recognition in the postero anterior projection. Lateral views are therefore necessary to delineate the atelectatic lobe. In some instances especially in

Figure 77A (*Upper left*) Bronchopulmonary segments right lung anterolateral view
Figure 77B (*Upper right*) Bronchopulmonary segments right lung medial view
Figure 77C (*Lower left*) Bronchopulmonary segments left lung anterolateral view
Figure 77D (*Lower right*) Bronchopulmonary segments left lung medial view
(For Nomenclature of Bronchopulmonary segments *see* Table 8)

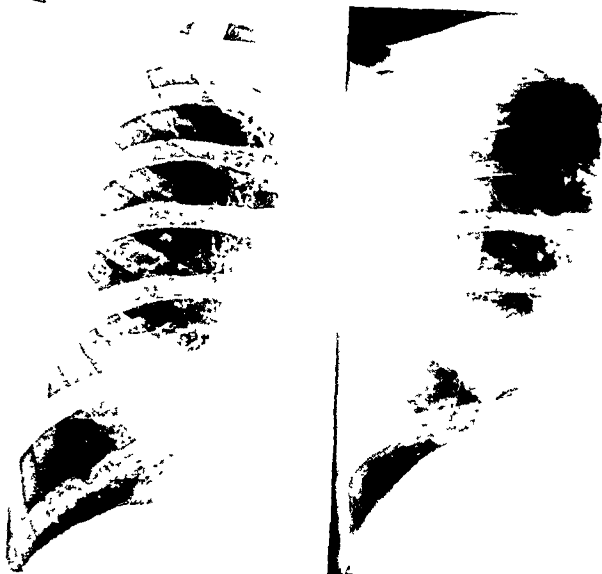
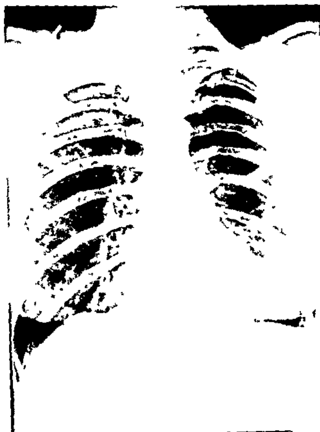


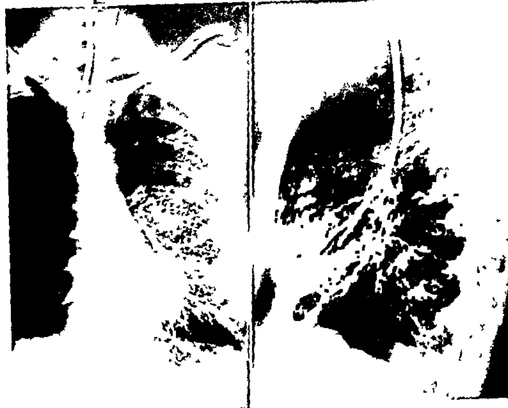
Figure 78 Demonstration of shrunken bronchiectatic right middle lobe A Irregular density in region of right middle lobe B Lordotic projection shows triangular density with a well demarcated lower border *(Continued on opposite page)*

Figure 78C *(Upper left)* Right lateral projection shows irregular triangular density in region of right middle lobe D *(Upper right)* Right lateral tomogram lateral section Middle lobe appears as a sharply triangular density *and somewhat quadrilateral in E (lower left) medial section F (Lower right) Bronchogram reveals* middle lobe bronchi moderately ectatic distal bronchi are free of oil entire middle lobe appears dense and contracted (Disease discovered accidentally in a forty four year old male course featured by occasional mild *respiratory infections) (From Rubin and Rubin Dis Chest, 38 327,* 1960)



(See legend on page 249.)





(See legend on opposite page.)

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over penetrated films the density of the contracted lobe may be sufficiently radiopaque to be discernible behind the heart silhouette In addition to the contraction of the involved mass collapse of a lobe is associated with dislocation of the major interlobar fissures which are depressed and shifted posteriorly In addition there is compensatory overdistention of the remaining lung as well as dislocations of the heart and mediastinum to one side or the other depending on the duration of the process and the presence or absence of an antecedent pleuritis

Roentgen Techniques

The procedures available in the roentgen examination of the chest comprise two major steps (1) screening (fluoroscopy) and (2) photographing the fluorescent image on a sensitized film (roentgenography) The latter may be accomplished in one of a number of projections utilizing various penetration and contrast techniques

Fluoroscopy

The place of this procedure in the detection of pulmonary disease depends to some extent on whether the examination is being conducted in the physician s office or in a hospital In hospital practice the routine postero anterior chest x ray serves as a scout film and fluoroscopy is utilized if the nature of the disease is not immediately apparent The fluoroscopic examination enables also the preselection of additional procedures which may be necessary to arrive at a diagnosis In office practice the fluoroscope is often the only x ray apparatus available The expert is able to glean considerable information from a fluoroscopic screening the less informed may obtain very little in fact so little that the examination may serve as a handicap by giving one a false sense of security Under no condition can fluoroscopy serve as a substitute for roentgenography since small lesions and even large ones are easily overlooked Furthermore fluoroscopy does not provide a permanent serial record which can be used in following the course of a disease This in itself is of inestimable value in prognosis

Felsen divides fluoroscopy into five phases which he designates as (1) observation (2) rotation (3) breathing (4) ingestion and (5) tilting The first letters spell the word ORBIT which serves as a mnemonic These phases are self explanatory They serve to disclose detail space relationships displacements and vascular lesions The last mentioned are brought out best through the Valsalva and Muller s maneuvers which have been described previously By these maneuvers it is possible to increase or decrease intrathoracic pressure thereby changing the size of the vascular channel

In the diagnosis of pulmonary lesions occurring in the course of systemic diseases fluoroscopy is seldom of much help excepting possibly in the diagnosis of pathological processes at the bases of the lungs which may be related to diaphragmatic or subdiaphragmatic disease In this respect it should be mentioned that if the diaphragm is normally placed and is freely movable with respiration it is very unlikely that one is dealing with disease involving the muscle The presence of discomfort during respiration associated with impediment in diaphragmatic excursion indicates that the lesion affects the peripheral portion of the muscle the only part which is pain sensitive In diseases associated with emphysema the low position of the diaphragm and its reduced excursion as well as the hyperillumination of the lower lung fields are best appreciated on fluoroscopy

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Figure 79 Demonstration of shrunken bronchiectatic lingula A (*Upper*) Haziness over left lower lung field blunting of costophrenic sinus B and C (*Lower left and right*) Bronchogram reveals dilatation of inferior bronchus of lingula (Female aged forty five years had empyema in childhood treated with thoracotomy and drainage course punctuated by occasional hemoptysis and recurring mild respiratory infections)

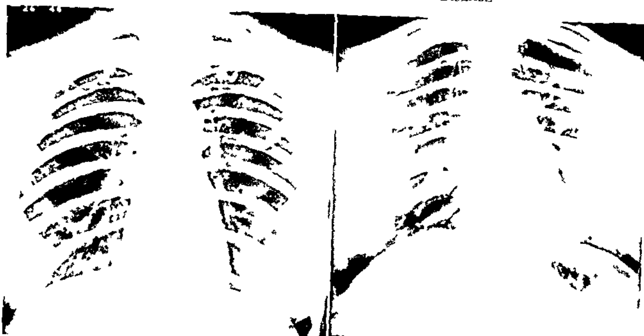


Figure 80 Demonstration of pulmonary tuberculosis with cavitation left upper lobe A (*Left*) PA projection shows a faint annular shadow in left upper lobe partly obscured by overlying ribs B (*Right*) Lordotic view shows the lesion as a clear cut cavity with a fluid level

Roentgenography

Projection Techniques

In the following pages the more important projection penetration and contrast techniques will be briefly defined No attempt will be made to enter into details because this is not the purpose of this book

Postero Anterior Projection This is the conventional position taken by persons in mass x ray surveys as well as in the routine chest examination The patient faces the cassette the tube stand is approximately six feet to the rear The patient is directed to take a breath and to hold it while the exposure is made There are occasions when an additional chest x ray exposure is indicated in the expiratory phase of respiration The latter serves to demonstrate small pneumothoraces localized areas of obstructive emphysema paralysis of the diaphragm and herniation of one or another of the weak spots of the mediastinum The amplitude of excursion of the diaphragm and the degree of illuminosity of the lower lung fields in the inspiration and expiration films provide a rough index of respiratory function

Antero Posterior Projection This position may be more accommodating to obese individuals with protuberant abdomens also to women late in pregnancy Apprehensive youngsters are often photographed better by facing the camera

Lordosis Projection The lordotic position allows better visualization of the apical regions of the lungs by dissociating the clavicles from the upper aperture of the thorax (Figure 80) Right middle lobe disease is also brought out better in this projection because the lobe and fissures are brought tangentially to the central ray

Lateral Projections This position reveals the interlobar fissures and parts of the lung which are poorly seen in the postero anterior projection This applies especially to the right middle lobe to the paravertebral retrocardiac and costophrenic sinuses The contents of the mediastinum and the contour of the diaphragm are also best visualized in this projection

Oblique Projections Oblique views in the anterior or posterior positions are helpful in visualizing lower lobe disease (Figure 81) When the bronchi are filled with radiopaque substance the right and left anterior oblique projections allow delineation of the tracheobronchial tree at

one sitting But the preferable way of demonstrating bronchiectasis especially if the possibility of surgical treatment is under consideration is to have each lung examined separately in the postero anterior lateral and oblique projections

Several additional projection techniques are available for specific purposes Chest x rays may be obtained with the patient lying on the back or side or in the Trendelenburg position by tilting the table so that the patient s head is at a lower level

Penetration Techniques *Body Section Roentgenography*

The Potter Bucky diaphragm technique is used in chest x ray examinations if rib involvement is suspected or if a thickened pleura or a thoracoplastic operation prevent visualization of underlying structures (Figure 82) A widely used technique is sectional roentgenography (tomography planigraphy laminography) By this means one is able to study serial sections of a lung with a minimum of interference of overlying structures The principle underlying sectional roentgenography is as follows the focal point of the tube moves in one direction as the film moves simultaneously in the opposite only the part of the chest under examination remaining constant The result is a well defined central area surrounded by blurred shadows outside the plane The lungs may be sectioned in the lateral as well as in the horizontal planes Sectional roentgenography finds important uses in delineating cavities or solid masses major tracheobronchial obstructions and cystic spaces in the lungs or pleura The procedure is especially useful in the examination of patients immediately prior to resectional surgery as well as after thoracoplastic operations



Figure 81 Demonstration of bronchiogenic cyst A (*Left*) PA projection shows suggestion of rounded density at the right border of the heart B (*Right*) Right anterior oblique projection reveals the density to be a large well circumscribed mass (At operation a bronchogenic cyst was found which was removed)

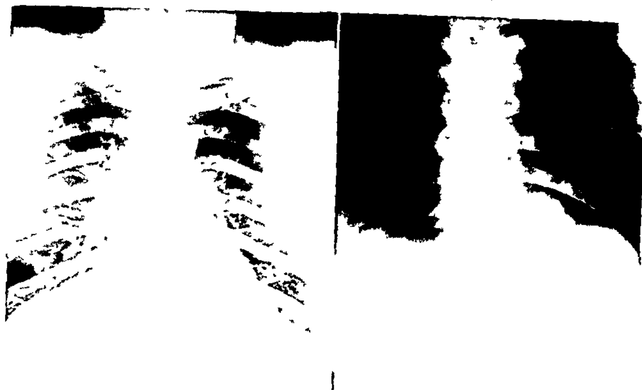


Figure 82 Demonstration of cyst A (*Left*) No significant abnormalities present in chest B (*Right*) Bucky shows ovoid density in lowermost portion of lung, adjacent to spine (At operation a multiloculated bronchiogenic cyst was found attached to left lower lobe, and to fundus of stomach through a small defect in posterior aspect of diaphragm removed successfully)

Contrast Techniques

Diagnostic Pneumothorax and Pneumoperitoneum The introduction of air into the pleural cavity provides a contrast medium which helps to offset any existing pleural or pulmonary density By separating the two layers of the pleura with air, one may determine if the disease is within the collapsed lung or in the pleura (Figure 83) If a pleural effusion is present, the fluid is aspirated and replaced by air Chest x rays are then taken in various projections, including lateral recumbent positions With increasing use of exploratory thoracotomy, the indications for diagnostic pneumothorax are becoming fewer The introduction of air into the peritoneal cavity permits the visualization of structures in the immediate vicinity of the diaphragm The procedure is occasionally indicated in the differential diagnosis of diaphragmatic hernia, eventration or phrenic nerve paralysis In the presence of ascites, the replacement of aspirated fluid by air is particularly helpful and practically devoid of danger The procedure permits visualization of the liver, spleen and other organs and, occasionally, the demonstration of metastatic deposits in the peritoneal cavity

Barium Meal This procedure is indicated in the diagnosis of lesions of the mediastinum and lower thoracic cavity which may be associated with or confused with lesions of the esophagus, stomach and the portions of the intestinal tract immediately beneath the diaphragm A barium meal is helpful in delineating obscure retrocardiac shadows, including esophageal diverticula, cardiospasm and diaphragmatic hernia (Figure 47)

Bronchography The instillation of a radiopaque medium into the bronchi is indicated in suspected bronchiectasis since a definitive diagnosis of this disease cannot be made on the basis of the clinical findings or routine chest x rays alone (Figures 84 and 85) Bronchography is also of value in marking out distorted or kinked bronchi bronchocavitary junctions, communications between bronchi and air cysts Instillation

of iodized oil helps to localize communications between bronchi pleura and skin Until recently *iodized oil was the medium generally* used but, because of certain disadvantages with this agent, chiefly the retention of the iodized oil in alveoli for considerable lengths of time, an aqueous medium is now being employed with increasing frequency It is beyond the scope of this discussion to dilate on the indications, contraindications, technique and other aspects of bronchography

Angiocardiography By rapidly instilling into an arm vein 25 to 35 cc of a 70 per cent solution of diodrast, and by taking chest x rays in rapid succession, the large blood vessels and chambers *of the heart are* visualized (Figure 65D) The technique of angiocardiography, perfected by Robb and Steinberg has met with universal acceptance in the study of cardiac dynamics as well as in diagnosis of diseases of the chest Angiocardiography is useful in delineating mediastinal lesions, abnormalities of the superior vena cava especially vena caval obstruction also arteriovenous aneurysms of the lungs fibrothorax and other diseases

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Figure 81 Diagnostic pneumoperitoneum A (Left) Right leaf of diaphragm ... displaced upward heart slight ... peritoneum the right leaf of ... of the liver is smooth and reg ... of diaphragm)



Figure 84 A (*Left*) Bronchogram showing saccular (cystic) dilatations of bronchi of right upper lobe B (*Right*) Lateral projection shows "saucer-shaped" puddling of iodized oil in affected bronchi, remaining bronchi appear uninvolved (From Rubin, Goldstine and Rubin *Med Clin North America*, 33 391, 1949)

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Figure 85 Segmental bronchiectasis A (*Left*) Irregular soft infiltrations in left lower lung field B and C (*Center and right*) Bronchogram in PA and left lateral projections show saccular and cylindric dilatations of bronchi in lingula and in superior segment of left lower lobe (Disease discovered after hemoptysis late in pregnancy)

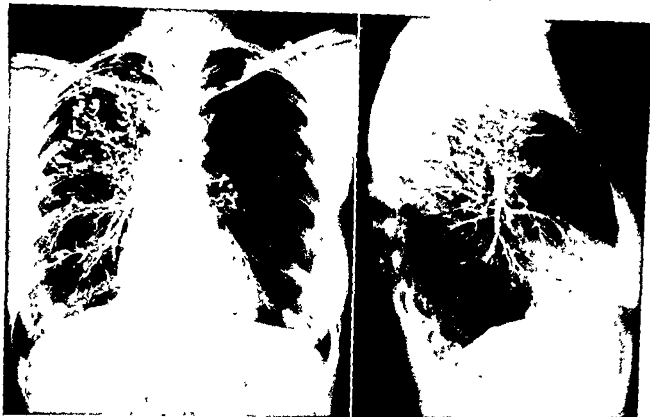


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Pitfalls in Roentgen Diagnosis

Introduction

HE "NORMAL" chest x ray reveals lung mark ngs which fall within a range of configurations ich as may be encountered in persons of the same ge, sex, etc. In the individual case however hat may appear as an innocuous looking lesion n one may connote serious disease in another A sion in the apex of a lung of an elderly white erson is apt to be considered of minor signifi cance. A similar lesion in a young Puerto Rican is more likely to represent active or potentially active pulmonary tuberculosis. What may appear as increased bronchovascular markings in one may indicate in another an early stage of silicosis or chronic passive congestion or sarcoidosis or sclerodermatous changes depending on the occu pation history, clinical and laboratory findings

The "Normal" Chest

The normal chest allows for considerable eviation from the norm before it falls within the ealm of distinctly abnormal depending on many actors technical as well as non technical A hest exposure taken of a crying child or of a erson who does not take a full breath may have he earmarks of an abnormal chest x ray unless ne is aware of the conditions under which the xposure was made Although the borderland etween the normal and abnormal is not wide rom a roentgenological standpoint it becomes ncreasingly so as more facts are known of the erson s sex occupation physical examination istory and laboratory findings and especially f one has some idea of what one is looking for

The physician who looks at a film for what ver it may reveal may see little, one interested in specific disease or detail as suggested by the istory and symptoms, may see a great deal The film is then no longer a composite of whites nd blacks but a delicate portrait possessing many ine shadings Undoubtedly there is a consider- able element of error if one attempts to see more han what meets the eye But the fact that the experienced radiologist is constantly asking for fuller briefing on the clinical findings proves that when a physician with a background of informa tion of a particular case looks *into* a film the pic ture is apt to be most revealing In other words, a chest x ray preferably serial x rays are much more informative if one suspects the presence of a certain disease than if one is simply on a fishing expedition This is the reason why mass chest x ray surveys can only serve as a means of screening large numbers of persons with the view of detecting lesions which after further studies may or may not turn out to be clinically signifi cant

The recognition of an abnormal chest x ray involves a complex mental process which with experience is reduced to a simple routine One notes immediately whether the disease affects primarily the thoracic cage or the soft structures including the heart and major blood vessels, mediastinum pleural cavity or lungs If chiefly in the lungs one notes whether the changes ap- pear to involve primarily the alveolar portions or the vascular system Although in many cases a clear cut differentiation of the various com ponents entering to the pathologic process can not be made a basic pattern is often apparent One takes into consideration the size location

configuration, manner of dispersion and the qualitative characteristics of the infiltrations One side of the chest is compared with the other In the presence of unilateral disease, one notes the position of the mediastinum and trachea, the heart, the diaphragm, in fact, all visible structures The previous chapter dealt at greater length with this phase of the subject For the moment, we are concerned chiefly with the limitations of the chest x ray and the sources of pseudopathological shadows Obviously an appreciation of the sources of error of chest roentgenography is a prerequisite for a proper evaluation of its reliability

Pitfalls in Diagnosis

The accuracy of chest roentgenography is determined by a number of variables those due to (1) failure of the chest x-ray to register disease, intrinsic errors', (2) discrepancies in film interpretation on the part of examiners which may give rise to 'subjective errors, and (3) failure of the chest x ray to record details with sufficient clarity or the presence of artefacts in the film which may be mistakenly ascribed to pathologic changes, leading to ' inherent errors in diagnosis

Intrinsic Errors

One or more of several factors may be responsible for the obtainment of a normal chest x ray in the presence of disease, with due regard to the many components which enter into the so called 'normal chest These are (1) the *time* it takes for certain disease processes to evolve to a state where they are discernible roentgenologically, (2) the *size*, *number* and, possibly *degree of opacity* which disease processes must attain before they can register roentgenologically and (3) the *site* of the disease

Latent Period in Roentgen Diagnosis

There are conditions affecting the lungs and appendages which cause roentgenographic changes almost immediately or within a few hours, if chest x rays are taken with sufficient frequency The conditions include acute pulmonary edema acute bacterial pneumonia massive atelectasis, as well as chest injuries The roentgenographic changes may precede symptoms and signs, as a rule, they follow the roentgenographic changes in rapid order Time in such instances, is usually not a decisive factor in diagnosis insofar as roentgenography is concerned On the other hand there are diseases which may require days, weeks and even months to make their roentgenographic appearance, an interval termed by Brailsford, the latent negative radiographic period" In view of the fact that symptoms and signs in many such diseases are often lacking especially in the initial stages, the delay in the appearance of abnormal changes in the chest x ray is a serious handicap

Rigler and Exner found that between the time of occurrence of the primary tuberculosis infection and the appearance of roentgenographic changes, a minimum latent period of from three to six months elapses The particular study was made on nurses in training in whom it was possible to determine the time of infection by noting the change in skin sensitivity from tuberculin negative to positive In a similar study, but utilizing comparative chest x rays alone, Louria found the average time between "negative' and ' positive' films to be five months Obviously, the interval depends on whether or not one is dealing with a primary infection, which holds true for many student nurses, or reinfection tuberculosis The latter takes less time to evolve because the element of hypersensitivity, the Koch phenomenon, comes into play Furthermore, much depends on the frequency and intensity of infection In any event, a variable period of latency occurs between infection and disease in tuberculosis during which interval the chest x ray may fail to reveal abnormal changes In suspected tuberculosis the factor of latency must therefore be taken into consideration in evaluating negative films, especially in dealing with nurses, physicians hospital personnel and others who may be heavily exposed to tubercle bacilli The vexing problem of tuberculosis developing in members of the Armed Forces shortly after induction, during the recent World War, in spite of negative preinduction chest x rays, was due in many in

stances to failure to take into consideration the factor of latency in the evolution of the disease

Number and Size of Infiltrations

In the normal chest x ray of a young person only the large blood vessels chiefly the pulmonary artery and its major divisions are visible The vascular markings give the lungs a web like appearance With age there is a variable degree of peribronchial and perivascular accentuation of markings The stringy striations are due to prominence of the accompanying lymphatics as a result of chronic irritation and low grade infections The smallest unit of the lung the primary lobule consisting of terminal bronchiole air ducts alveoli and supplying blood and lymph vessels do not cast shadows unless they are diseased

William Snow Miller estimated that from 50 to 750 anatomic units are present in a secondary lobule the latter measuring from 1 5 to 2 5 cm in diameter Since in the usual instance of inflammatory reaction it is necessary to have involvement of one or more secondary lobules for roentgenographic portrayal it is evident that disease of appreciable size has to be present before it can be visualized grossly This feature is exemplified in the evolution of miliary tubercles Although the lungs possess a dual blood supply and are ideally placed to mirror a hematogenous dissemination of foci the chest x ray may fail to reveal miliary deposits Roentgenographic evidence of miliary tuberculosis is encountered in only one third of patients whose lungs reveal tubercles at autopsy Of course in many instances such tubercles represent terminal seedings It is well to point out that generalized miliary tuberculosis is not necessarily a disease of infancy and childhood The disease may occur at any age and is not at all infrequent in individuals of advanced years

One of the major reasons why the lungs may fail to disclose in the chest x ray the characteristic symmetric dispersion of tubercles in miliary tuberculosis is because the foci have to reach a certain size and number before they are visible in the roentgenogram Emery and Lorber found chest x rays positive within two weeks of death if the majority of the tubercles were over 1 mm in diameter and their number 5 to 20 per cm In the roentgenologically negative group the tubercles were mostly under 0 5 mm wide and their numbers ranged from 1 to 6 per cm [2] These investigators found no direct relationship between the histological structure of the tubercle and its roentgenological portrayal Most observers hold similar views although it would seem offhand that the harder the tubercle (one containing a predominance of fibroplastic elements and collagen tissue) the more easily it should be discernible especially since calcification increases with maturation of the tubercle Studies by Bloch indicate that the presence of calcium salts in a tubercle is not a reliable index of its roentgen visibility He found that lesions containing considerable amounts of calcium may possess a lower roentgen density than noncalcified pulmonary foci

Metastatic neoplastic deposits may likewise escape roentgenological detection unless the individual foci are of appreciable size and number Fairly large metastatic lesions may be invisible A patient with an alveolar cell carcinoma was examined at autopsy at the Bronx Municipal Hospital Center and the lungs revealed fairly large metastatic deposits which did not register in a recently taken chest x ray On the whole metastatic foci because of their uneven size and distribution are recognized easily and at a fairly early stage of development Surprisingly Lee found metastases in the lungs of thirty patients of a total of seventy nine examined at autopsy in whom chest x rays taken within three weeks of death had failed to disclose the pulmonary deposits

With the introduction of body section roentgenography and with increasing use of excisional surgery the frequent failure of the routine chest x ray to reveal disease has been forcefully brought to the attention of those engaged in the diagnosis and treatment of pulmonary diseases especially tuberculosis At best the chest x ray shows only the major focus or an aggregate of small foci Consolidations of appreciable size may be missed in conventional chest x rays This applies also to cavities Examination of surg

ically excised tuberculous lung tissue almost invariably shows much more disease than is revealed in chest x-rays taken shortly before operation What appear to be slight changes may be quite deceptive

It is well to point out that not all annular rarefactions seen in conventional chest x rays, or even sectional x-rays, represent cavities in the lung In a recent comparative study of chest x rays and excised lobes or lungs done at Seton Hospital to be referred to later many specimens were found which failed to show cavitation although strongly suspected on the basis of the chest x ray findings An irregular group of tuberculous foci accompanied by regional emphysema may simulate intrapulmonary cavities With the introduction of specific antibacterial agents in the treatment of tuberculosis, it has become necessary to reorient one's thinking regarding roentgenological morphological equivalents A tuberculous process undergoing healing under the effects of antibacterial treatment and in due time resected, no longer reveals the type of pathological changes one has been accustomed to see at autopsy and upon which roentgen interpretation had been based in previous years

Site of Disease

The portions of the lungs which offer the most difficulties in roentgen interpretation of disease are the bronchi, the corticopleural layer, the vascular and perivascular tissues However the physician's attention is often directed to these possible sites of involvement by symptoms and physical signs Cough and variable degrees of expectoration occasionally hemoptysis and wheezing rales, feature bronchial disease A localized wheeze often accompanies bronchial obstruction Chest pain and friction rub often accompany pleural disease In addition there are various diagnostic means available to supplement routine roentgenography

In the presence of partial bronchial obstruction, a chest x ray taken in complete expiration may reveal a localized area of hyperillumination due to localized emphysema Following complete occlusion of the bronchus there is atelectasis of the involved bronchopulmonary segment In the presence of infection distal to the bronchial obstruction, and the development of lung abscess, the rapid changes in serial chest x-rays may be quite striking Sectional roentgenography in frontal, lateral and, at times eccentric planes is a useful aid in diagnosis of pulmonary tuberculosis, bronchiogenic neoplasms and other conditions

The interior of the main bronchi may be examined bronchoscopically and, at the same time, specimens obtained for bacteriological and cytological studies Bronchography is a valuable means of visualizing the smaller radicles of the bronchi in suspected bronchial obstruction as well as in bronchiectasis But one must be on guard in using iodized oil in the presence of a bronchial block lest the oil be retained and incite a foreign body reaction The current use of a quickly absorbable radiopaque substance in watery solution is superior although slightly more irritant and the contrast not as definitive

Disease concentrated at the periphery of the lung is rarely diagnosable during life although such involvement occurs during the evolution of a number of conditions notably lymphohematogenous tuberculosis and carcinomatosis If there is an exudate in the pleural cavity and diffuse reticulation of the lungs, especially along the interlobar fissures one may suspect associated corticopleural involvement It might be mentioned at this point that Rigler has shown that in the average adult chest as much as 300 cc of fluid may be present and be unrecognized in the conventional postero anterior chest x-ray Even in the lateral projection this amount of fluid may not be clearly visible Chest x rays taken with the patient in the lateral recumbent position will reveal free fluid in amounts as low as 100 cc

Involvement of the pulmonary blood vessels, with minor degrees of parenchymal disease demonstrable grossly, may manifest itself (1) in alteration of the walls of the blood vessels as in syphilis arteriosclerosis or septic processes, (2) in vascular engorgement, cardiorenal disease, hypetergic states or as a result of toxic irritation of one type or another, and (3) in obstructive phenomena due to thrombosis or embolism of larger

blood vessels or endarteritic occlusive changes of smaller blood vessels. Sudden occlusion of a main pulmonary artery by embolism without infarction may reveal itself roentgenologically in an increased transparency of the involved lung segment as a result of the disappearance of the normal vascular pattern by ischemia (Westermark). As a rule, symptoms and signs of anoxia as well as other evidence of cardiopulmonary insufficiency are present to draw the physician's attention to the possible involvement of the pulmonary blood vessels.

Diffuse interstitial fibrosis of the lungs, almost invariably associated with variable degrees of alveolar wall thickening, as well as conditions associated with vascular and perivascular changes characterize a number of systemic diseases. The structural alterations are usually not demonstrable roentgenologically unless pronounced. An associated hyperillumination of the lung parenchyma tends to obscure the fine nodulations in the chest x-ray. A number of systemic diseases previously described, manifest themselves in this type of tissue reaction in the lungs.

Subjective Errors

Since roentgenography is not an exact science, it is not surprising that discrepancies should arise in the interpretation of chest x-rays not only between readers but also by the same reader on reviewing the same films. In addition to faulty judgment, sources of error lie in fatigue and lack of concentration on the part of the examiner. Statistical studies by Yerushalmy and his co-workers have served to emphasize the important role played by the, so called "personal equation" of the examiner. There is a large field of inter-individual as well as intra-individual disagreement. These investigators found that, in some instances as much as 20 per cent of the films read "positive" for tuberculosis by one reader was read "negative" by another.

Although differences in readers' background and experience may explain in part the variations in roentgenographic interpretations, they do not account for the fact that the same individual may disagree with himself in reviewing the same films. In an example cited by Yerushalmy, the first reading revealed fifty-nine films "positive" for tuberculosis, on the second reading 7 per cent of these were found "negative" and an additional 3 per cent "essentially negative." On another occasion the same physician read seventy-eight cases "positive" for tuberculosis of which 29 per cent had been "negative" on the first reading and an additional 29 per cent "essentially negative."

In another investigation, the field of disagreement was even more impressive. The particular study dealt with an evaluation of the role of serial chest x-rays in estimating the progress of disease in patients with pulmonary tuberculosis. From this study it appeared that the radiologists on the panel were more consistent in their interpretation than were the chest specialists. The latter in their intuitive attempt to read into the film were "more inclined to observe improvement in two films than were the radiologists, while the latter were more likely to diagnose stability in the film pair than were the chest specialists." In other words, not knowing the clinical status of the patient, the radiologist is apt to take a noncommittal attitude in questionable cases, the physician, accustomed to view the film from a clinical standpoint, is inclined to take more liberties in interpretation.

Objectivity on the part of the reader may be carried to an extreme. It is common experience that although no significant changes may be discernible in chest x-rays taken at short intervals, one often finds significant degrees of improvement or deterioration when one reviews a series of chest x-rays taken over an appreciable period, especially if one is fortified with knowledge of the clinical course of the disease. In reviewing the progress of a case it is essential to examine the first available chest x-rays as well as the most recent ones.

The studies previously cited by Yerushalmy and his co-workers were undertaken primarily to test the reliability of roentgenographic interpretation in mass chest x-ray surveys. As was mentioned previously, such mass surveys simply serve to orient the examiner as to the need of additional examinations in particular cases. The studies demonstrate the fallacy of considering a chest x-ray self sufficient. They also serve to emphasize the importance of having at least two

independent readings made in the conduct of mass chest x-ray surveys

Clayson and co workers investigated the relative value of miniature (70 mm) films and large films in the roentgenological diagnosis of pulmonary tuberculosis They found that "within reader" variability (inconsistency in readings regardless of "truth"), was nearly as great with large films as with small films "Between reader" variability was, if anything, greater on large films than on small films Accuracy (agreement with "truth") was better in readings of large films but even on large films readings, loss of genuine cases was considerable These investigators found that accuracy decreased when attempts at increased precision of diagnosis were made, and was especially low in attempted diagnoses of "activity" of lesions Similar conclusions were reached by Newell and co workers with respect to qualitative description of disease

In an attempt to measure the reliability and validity of roentgenographic diagnosis in the field of tuberculosis, in order to arrive at a practical descriptive classification of pulmonary lesions as seen on the roentgenogram Newell, Chamberlain and Rigler restudied the problem from various angles including the extent of the disease, qualitative description of the pathologic process and an estimation of "activity" They came to the conclusion that a classification of possible tuberculous pulmonary lesions, on the basis of roentgenographic appearances, is not very reliable They found little to choose among three approaches to the problem (a) an objective description of the lesion, (b) a quasi pathologic classification, and (c) a subjective judgment of activity All were less reliable than the classification of extent of disease in common use (minimal, moderately advanced, far advanced) These investigators concluded that a subjective (intuitive) judgment of activity appeared to be about as reliable as is a description and classification of the objective appearance of the lesion on the film But in spite of their experience, they still felt convinced that the qualitative appearance of a lesion, as seen on a chest film, must have clinical significance

In a study of 190 patients with pulmonary tuberculosis who had been treated with resectional surgery at Seton Hospital, Kothari, Shah and I attempted to compare the chest x ray findings plus whatever information could be obtained from the clinical, bacteriological and bronchoscopic findings and the pathology of the excised specimen This correlative study was applied with special reference to the presence or absence of cavity and to the presence or absence of tuberculosis of small bronchi The existence of the latter is often characterized by a triangular distribution of linear markings and contraction of the involved segment or lobe It might be added, that with respect to the diagnosis of endobronchial tuberculosis, considerable weight was placed on bronchoscopic and bacteriological findings

The results were quite instructive In 82 specimens in which "gross" cavitation was found in the specimen, the presence of antra was suspected in sixty seven (82 per cent), in 102 specimens in which "gross" cavitation was not found (some had small, blocked cavities and, so called, tuberculomas), cavitation had been suspected clinically in twenty (20 per cent) In other words, in approximately 20 per cent of tuberculous cavities, the diagnosis was incorrect, false positive results being obtained as often as false negative results A recent study by Mayock and co workers revealed similar results In ten of eleven lung specimens removed surgically from patients with tuberculosis, areas of translucency were produced by lesions which were filled with solid or liquid caseous material These areas simulated cavitation or localized emphysema on standard chest x rays These investigators suggest that the development of these areas of translucency may result from a physiochemical change in caseous or necrotic tissue, possibly due to a lipid type of degeneration

In the diagnosis of endobronchial tuberculosis, in which a subjective factor plays a particularly important role, the accuracy of suspicion was approximately the same as that applied to cavitation In 102 specimens in which significant degrees of tuberculosis were found in the small bronchi, the presence of such involvement was suspected in eighty-three (82 per cent) However, endobronchial tuberculosis was present in nineteen of ninety specimens (21 per cent) in

which the disease had not been suspected clinically It would seem therefore, that in the interpretation of chest x rays insofar as it applies to pulmonary tuberculosis, with or without cavitation or endobronchial disease, there is considerable room for error

Inherent Errors

In addition to the many technical factors involved in the exposure and processing of the x ray film and which may spell the difference between a readable and an unreadable product, there may be encountered abnormal shadows of increased density caused by artefacts, some easily recognized, others giving rise to misinterpretation Morgan and co workers also Hefke, have drawn special attention to some of these 'inherent errors" Artificial shadows may be caused by pins, medals, necklaces, buttons and other opaque substances Such objects are frequently encountered in chest x rays taken in mass surveys of persons wearing part of their clothing during the exposure The experienced reader soon learns to discount these pseudopathological shadows In hospital practice artificial chest shadows are also often encountered in patients with heavy dressings fixed by adhesive tape These extraneous shadows are distinguished by the fact that they extend beyond the confines of the lung fields Sources of error may be encountered if one fails to have hair braids pinned up or to recognize and make note of obvious chest deformities such as kyphosis, scoliosis, pectus excavatus and other abnormalities

One has to be on guard against artefacts or pseudopathological shadows because their misinterpretation may be a source of much anguish to the patient and embarrassment to the physician I have in mind instances of persons who have had routine chest x-rays and who were *told* to see their physician because of some abnormalities found The initial chest x ray may show opacities which depending on their location and the age of the patient, may be suggestive of tuberculosis, neoplasm or some other disease Retake films may fail to demonstrate these opacities The original film, when carefully examined may show the 'abnormal' markings to be due either to pressure marks" or uneven emulsification of the film or failure to recognize an artefact of one cause or another But once a person is told that an abnormal shadow is present in the chest x ray, especially after an examination in a cancer detection or tuberculosis clinic it takes a great deal of persuasion on the part of the physician, often several physicians, before the patient's anxiety is relieved

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Chapter 16

Laboratory and Exploratory Aids

Introduction

THE preceding chapters referred briefly to certain laboratory tests commonly employed in the diagnosis of systemic diseases which may be associated with pulmonary lesions The following will deal with laboratory diagnosis from the viewpoint of the pulmonary lesions themselves In the differential diagnosis of such lesions, laboratory tests are utilized to help identify the causative agent, if possible *But, inasmuch as the* determination of the cause may be quite difficult, *the laboratory is used for a broader survey than* might be deemed necessary under ordinary circumstances *At best, the laboratory findings have to be evaluated in the light of the clinical* picture as a whole

In the differential diagnosis of diffuse pulmonary lesions the examination of the sputum, blood, urine and body fluids serves to direct attention to the existence of a generalized disturbance The results of such tests are seldom conclusive because the laboratory findings vary at different stages of a disease and the results are more apt to apply to a related group of disorders than to a single one This feature applies especially to the collagen and hyperergic groups of diseases and, to variable degrees, to most of the conditions described in these pages To establish *the presence of a specific abnormality, one has to* depend on the examination of tissues obtained *from lymph nodes, skin, bone marrow, liver and* other parts of the body In the absence of demonstrable pathologic changes in the organs and tissues mentioned, it may be necessary to resort to lung biopsy and, occasionally, to exploratory thoracotomy Even these may not provide the final answer for the reason that pulmonary lesions occurring in a protracted illness, are often transitory phenomena in an undulant disease and the time of appearance of various organ and tissue involvements may have to await further developments

Examination of the Sputum

BACTERIOLOGICAL FINDINGS

The discovery of a pulmonary lesion in a patient with a systemic disease or, for that matter, under any circumstances calls for a careful bacteriological examination of the sputum for acid fast bacilli and other organisms Although the sputum findings seldom permit of a specific diagnosis, negative results are of considerable value in ruling out a number of conditions which may closely simulate the type of pulmonary lesions under investigation

EXAMINATION FOR *TUBERCLE BACILLI AND* OTHER BACTERIA

The examination of the sputum for tubercle bacilli is of prime importance since pulmonary tuberculosis enters into the differential diagnosis of practically every disease which may affect the lungs and appendages Until recently, one could subscribe, with few reservations, to the statement that the demonstration of acid fast bacilli in the sputum or gastric washings of a patient with roentgenologically demonstrable pul

monary disease indicates active pulmonary tuberculosis. With almost equal assurance, one could state that failure to find acid fast bacilli on repeated examinations rules out the presence of active pulmonary tuberculosis. These *ex cathedra* pronouncements are no longer tenable. Under the effects of streptomycin, isoniazid and several of the other antituberculosis agents commonly in use today, there is early suppression of growth of the tubercle bacillus. The organisms may be seen in smear but they may fail to grow out in culture and, as a result of loss of virulence, the bacilli may be incapable of infecting susceptible animals. It is now realized that active pulmonary tuberculosis may be associated with "negative" sputum or gastric washings and inactive tuberculosis, with "positive" sputum containing nonvirulent tubercle bacilli.

A pressing issue, at the moment, are two phenomena which the physician has to be prepared to encounter in pulmonary tuberculosis, either as a newly acquired disease or as a complication of an existing ailment. It is a matter of common knowledge that pulmonary tuberculosis may complicate malignant neoplasms, the lymphomas, especially Hodgkin's disease, bronchial asthma, disseminated lupus erythematosus, sarcoidosis and several of the other diseases described in these pages. What is not generally known is the fact that prolonged use of steroid hormones currently being employed in the treatment of these conditions, is associated with the added danger of an outbreak of an acute pneumonia, nontuberculous as well as tuberculous, which may not become immediately apparent because of the masking effect of ACTH and cortisone on infection. Steroid therapy is known to suppress acute inflammation, inhibit repair and increase blood coagulability. These factors favor the development of "silent" pneumonias until they reach explosive stages.

The number of patients developing acute bacterial and fungous infections of the lungs, also caseous and miliary tuberculosis, under the effects of steroid therapy, is increasing. In view of this danger, as a precautionary measure, it is advisable to administer 1 Gm. streptomycin, once or twice weekly, plus 200 mg. isoniazid daily to all patients under steroid treatment for diseases which are known to be frequent precursors of pulmonary tuberculosis, especially if the lungs reveal what may appear to be inactive foci. By the same token, patients under prolonged steroid treatment for rheumatoid arthritis and other diseases should have frequent chest x-rays to make certain that the lungs do not become the seat of silent infections.

Examination for Fungi, Parasites and Other Abnormal Agents

The systemic diseases which may be associated with diffuse interstitial pulmonary lesions, or with disseminated foci of bronchopneumonia or calcification, often bring to mind the possible presence of a fungous infection. The latter may be a complicating factor as a result of prolonged use of antibiotics or steroid therapy which many patients with pulmonary diseases of the types under consideration are apt to receive. The more common fungous infections which may affect the lungs of human beings are actinomycosis, the blastomycoses, coccidioidomycosis, histoplasmosis, cryptococcosis (torulosis), geotrichosis, nocardiosis and candidiocosis (moniliasis), especially the last mentioned.

The simplest laboratory test for the detection of fungi in sputum is direct examination of stained and unstained wet mounts. Schiff's periodic acid stain is a dependable method of demonstrating fungi. Sabouraud's glucose-agar medium, with the addition of antibiotics, is widely used for routine cultures. Special stains and media are utilized for the detection of individual species.

As mentioned, the recognition of the bronchomycoses, especially moniliasis, has become a serious consideration since the introduction of the antibiotics. The elimination of the normal bacterial flora of the mouth and upper air passages, after prolonged use of potent antibiotics, results in an overgrowth of normally nonpathogenic yeasts and fungi, also in disturbances of vitamin metabolism. In a study of moniliasis of the mucous membranes and lungs, as a complication of treatment with antibiotics, corticotropin and cortisone, Bradlund and Holten found that moniliasis developed in eight of 103 patients who had



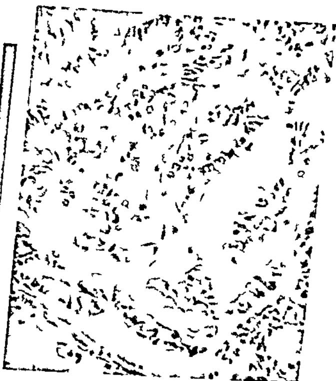
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received corticotropin or cortisone and in seven of 107 patients who had received antibiotics in addition to these hormones In three additional cases moniliasis was encountered as a complication of antimicrobial treatment alone In the mild cases the discontinuation of cortisone or corticotropin was not necessary In the more severe cases the hormones were withdrawn gradually The treatment of moniliasis consisted of careful attention to nutrition and oral hygiene Parenteral administration of vitamin B complex also appeared to be of value

Patients presenting diffuse pulmonary lesions may be found to have parasitic organisms in the sputum This is true especially of diseases associated with eosinophilia The life cycles of Ascaris lumbricoides Strongyloides stercoralis and Paragonimus westermanii involve the lungs either in the larval stages or as mature parasites Special importance has been ascribed to mites (Acarina) in the evolution of bronchopulmonary infections associated with eosinophilia (see Chapter 5)

The sputum may also contain various formed and unformed elements including caseous material and broncholiths the latter resulting from perforation of bronchi by broken off particles of caseocalcareous lymph nodes Carbon matter foreign bodies food debris hair from ruptured dermoid cysts and bronchial casts may also be eliminated in the sputum The sputum should also be examined for fat droplets Losner and co workers found lipid material in the sputum of nineteen of twenty patients suspected of having lipid pneumonia and in only two of forty five patients of a control group All but two of the patients of the former had previously taken mineral oil or nose drops either continually or at intervals over periods ranging from two to thirty years These investigators found that the sputum could be considered positive for oil if the Wright stain demonstrated characteristic vacuoles and macrophages and if these vacuoles stained orange brown with Sudan 4 or if abundant extracellular fat staining material was noted Although in most instances one is dealing with aspiration lipid pneumonia occasionally the condition turns out to be an intrinsic form of disease of the type described in Chapter 3

Exfoliative Cytology

In the differential diagnosis of diffuse pulmonary lesions the possibility of a pulmonary neoplasm also comes into consideration Primary bronchiolar carcinoma or so called pulmonary adenomatosis as well as metastatic malignancies have to be differentiated from nonmalignant systemic diseases with pulmonary lesions It should be noted that a pulmonary neoplasm may be present coincidentally with a systemic disease and that what may appear to be a systemic disturbance may be caused by a silent malignancy of the lung The examination of the sputum and bronchial aspirates for exfoliative cytology, i e cells shed from surfaces of organs into surrounding fluid is an important step in differential diagnosis of every obscure pulmonary disease

Considerable advances have been made in recent years in the diagnosis of pulmonary cancer by cytologic examination of sputum and bronchial washings Improved methods of obtaining fixing and staining smear preparations have contributed largely to the acceptance of the results of exfoliative cytology, not only in the diagnosis of pulmonary neoplasms but also as a screening device in the examination of persons in cancer detection clinics for the possible presence of cancer of the female genital tract, breast and other organs With respect to the cytological diagnosis of pulmonary malignancies some investigators have found no advantages in the results obtained from bronchial washings as compared to sputum smears

Malignant changes in sputum or bronchial aspirates are looked for especially in cell nuclei

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Figure 86 Exfoliative cytology A Circumscribed density in left lower lobe B Bronchoscopic washings reveal nests of tumor cells arranged in a pseudoglandular pattern acini are lined by hyperchromatic low columnar cells of varying size and shape possessing huge atypical and variegated nuclei cytoplasm of cells is scanty C Well circumscribed mass in resected left lower lobe D Tumor shows pattern of adenocarcinoma composed of large irregular gland acini with many infoldings and plications lining cells are similar to those seen in bronchoscopic washings

with respect to size, hyperchromasia, prominence of nucleoli, irregular mitotic division and other abnormal changes (Figure 86) Nuclear atypia constitutes one of the earliest signs of malignancy Uninjured cells, occurring in clumps, are apt to be most revealing but even the appearance of single cells may be informative Experienced pathologists have been able to distinguish specific types of cancer cells but many are loathe to make such distinctions because of the pleomorphic nature of pulmonary malignancies Foote has been able to differentiate types of cancer cells in as high as 80 per cent of sputum smears and bronchial washings Paradoxically, this investigator found that sputum smears allowed better recognition of the type of tumor cell than did the bronchial aspirates

It should be emphasized that atypical cells highly suggestive of malignancy, may be found in the presence of chronic pulmonary suppuration It should also be mentioned that metastatic carcinoma of the lungs may likewise give rise to cancer cells in sputum and bronchial washings (Figure 87, *cf* Figure 59) False positive cytological diagnoses of cancer vary in the hands of different observers The average ranges between 2 and 3 per cent but false positive tests have been reported in as high as 10 per cent In spite of the great advances made in exfoliative cytology, a field to which Papanicolaou has made notable contributions, a definitive diagnosis of cancer depends on tissue examination Although positive cytological findings may offer an added indication for exploratory thoracotomy, the need of resection and the extent of the latter is dictated by the findings at operation

Examination of the Blood

It is beyond the scope of this book to enter into a detailed discussion of the various blood examinations which may be found helpful in the diagnosis of pulmonary lesions associated with systemic diseases Suffice it to underline a few tests relating to several of the conditions described In general, blood examinations seldom supply information as to the exact nature of a disease, excepting those involving primarily or chiefly the hemopoietic system However, the blood picture may be sufficiently distinctive to apply to a related group of diseases and, what is equally important, repeated blood testing is often of prognostic value

The Erythrocyte Sedimentation Test

The erythrocyte sedimentation test, although nonspecific, is used extensively as an index of activity of disease, especially if the latter is associated with gross inflammation or destruction of tissues If the cause of the latter is unknown an accelerated sedimentation velocity of erythrocytes serves to draw attention to the possible presence of a disease which might otherwise escape recognition because of the absence of symptoms or vital signs If the cause is known, and due allowance is made for any associated anemia, which in itself increases the settling velocity of erythrocytes, the test possesses prognostic value as an indicator of the course of events and the response to treatment

It is good practice to inspect the sedimentation tubes the morning after the blood sampling By this time, the blood has differentiated itself into three distinct layers plasma, white cells and red cells The color, appearance, and turbidity of the plasma are often revealing, the former reflects the bilirubin content, the latter, the protein content The height of the white and red cell layers are roughly proportional to their respective cell volumes In patients with significant leukocytosis the white cell layer is noticeably deeper as compared to layers in the comparison test tubes I have come across two cases in which an unusually high column of leukocytes led to further studies and a diagnosis of leukemia

The erythrocyte sedimentation test is most useful in following the course of prolonged illnesses especially tuberculosis malignancies and rheumatic fever The test is also of value in acute and subacute hyperergic, rheumatoid and collagen diseases The increase of highly labile globulin components of the sera and resulting reversal of the A/G ratio, commonly encountered in these conditions, is associated with rapid blood sedimentation In fact, the changes in the

serum proteins in the diseases mentioned are the bases of a number of serum and plasma colloid lability tests. The alterations in serum proteins may even cause false positive serologic tests and are believed to be a factor in L.E. cell formation. False positive Wassermann tests have been found in as high as 16.8 per cent of cases of disseminated lupus erythematosus, in 10.6 per cent of cases of polyarteritis nodosa and in 6.6 per cent of cases of rheumatoid arthritis.

Cytological Findings

Reference was made in Chapter 4 to certain pulmonary diseases, notably tuberculosis and malignant neoplasms, which may be associated with hemolytic anemia, leukemoid reactions, leukopenia and other atypical blood findings. Leukocytosis, with a shift to the left, is common in rheumatic fever, during acute exacerbations of rheumatoid arthritis, in polyarteritis nodosa and dermatomyositis. On the other hand, disseminated lupus erythematosus is more often associated with leukopenia and thrombocytopenia, unless there is superimposed infection in which case variable degrees of leukocytosis may appear. Although an excess of eosinophils in the blood (more than 300 cells per cu. mm. or more than 5 per cent in the differential count) is a feature of most allergic states, the absence of eosinophilia does not rule out allergy. Eosinophilia, as shown in Table 9, is encountered in a variety of diseases including dermatologic disorders, parasitic infestations and various infections. An excess of eosinophils is also seen in dermatomyositis and occasionally in eosinophilic granuloma.

TABLE 9

Causes of Eosinophilia

1. Allergic disorders: bronchial asthma, urticaria, angioneurotic edema, hay fever
2. Skin diseases, especially pemphigus and dermatitis herpetiformis
3. Parasitic infestations, especially parasites which invade the tissues, e.g., trichinosis, echinococcus disease; less regularly in intestinal parasitism
4. Certain infections, e.g., scarlet fever, chorea, erythema multiforme
5. Certain diseases of the hemopoietic system: chronic myelocytic leukemia, erythremia, Hodgkin's disease, after splenectomy, pernicious anemia
6. Following irradiation
7. Miscellaneous disorders: periarteritis nodosa, tumors of the ovary or those involving serous surfaces or bones, certain poisons
8. Loeffler's syndrome, "tropical eosinophilia"
9. As a familial anomaly

(From Wintrobe: *Clinical Hematology*, 3d Ed. Philadelphia, Lea & Febiger, 1951.)

The L.E. Test

In the discussion of disseminated lupus erythematosus, reference was made to the significance of the finding of L.E. cells in the peripheral blood and/or bone marrow (Figure 30B). It is becoming increasingly apparent that the L.E. test is highly specific. Noteworthy is the fact that presumably false positive tests are met with under circumstances which of themselves add importance to the significance of the phenomenon. Of a total of 4200 examinations Lee obtained seventy-two positive L.E. tests. Sixty-six of these had demonstrable disseminated lupus erythematosus. In the remaining six there were suggestive but not conclusive indices of the disease. These six included patients who showed one or more features commonly associated with lupus, such as rheumatoid arthritis, arthralgias, hemolytic anemia, leukopenia, thrombocytopenia, unexplained facial rashes, false positive serologic test for syphilis and the like. Lee encountered one patient with interstitial pulmonary fibrosis in whom a positive L.E. test was obtained and only one of proved disseminated lupus erythematosus associated with a negative L.E. test.

Weiss and Swift studied L.E. preparations in 350 patients. L.E. cells were found only when lupus erythematosus was the leading or possible diagnosis. In agreement with others, these investigators suspect that disseminated lupus erythematosus is probably a phenomenon of hypersensitivity. There is some evidence that the L.E. phenomenon depends on an antigen-antibody mechanism found in patients with a high serum globulin, possibly a distinct gamma fraction. Reference was made elsewhere to the reported occurrence of L.E. cells in association with penicillin reactions, pernicious anemia, dermatitis herpetiformis, multiple myeloma, miliary tuberculosis and leukemia. Joske and King reported the finding of L.E. cells in the blood from two patients with active chronic hepatitis probably of



Figure 87 ...
ings and p...
prominent

Figure 88 Section through skin Subcutaneous tissue shows poorly circumscribed granulomatous lesion with mononuclear and occasional giant cells, consistent with positive Kveim test

viral origin It should be noted that the L E test may be negative in patients under steroid treatment Weiss and Swift suggest that all patients with rheumatoid arthritis should have frequent L E tests done, even if they show minimal symptoms suggestive of lupus erythematosus For reasons mentioned in Chapter 6, this applies also to patients with diffuse interstitial pulmonary fibrosis

Skin Tests

In the differential diagnosis of disseminated pulmonary lesions, occurring in the course of systemic diseases, there is occasional need for skin tests Skin testing is indicated in suspected tuberculosis, sarcoidosis, fungous infections and diseases of hypersensitivity

Tuberculin Skin Test

With the marked decrease in the mortality and, to a lesser degree, morbidity from tuberculosis in the past few years, the tuberculin test has assumed greater importance The extremely low infection rate of tuberculosis in children has relegated to the background the value of skin testing as a case-finding method since the occasional positive reactor hardly pays for the time and effort involved *Pari passu*, the use of tuberculin *is becoming increasingly valuable as a diagnostic test since a positive test indicates probable recent infection with tuberculosis* and points to a possible source of contact at home Chest x rays of contacts often lead to the discovery of active tuberculosis in a member of the family

The incidence of false positive reactions to

tuberculin increases as the dose is increased. A significant percentage of reactions following the second strength PPD (purified protein derivative) are nonspecific. A positive skin test after the first dose of PPD is, therefore, more informative. On the basis of exhaustive investigations, Edwards and co-workers found that a definite induration of the skin, of 5 mm. or more, after inoculation of 0.0001 mg. of standard PPD tuberculin, is specific for infection with tuberculosis. A depression of skin sensitivity to tuberculin may result in false negative reactions during measles, influenza, brucellosis and pregnancy. The lowering of skin sensitivity to tuberculin in *these conditions holds true for other skin antigens*. In fact, the occurrence of negative tuberculin skin reactions in patients with sarcoidosis is ascribed to a similar immunologic mechanism. It should be mentioned that the use of streptomycin and isoniazid has raised some doubt as to the reliability of tuberculin skin testing when patients are receiving antituberculosis drugs. A marked decrease and even a reversion of tuberculin hypersensitivity has been observed in experimental animals treated with these agents. Recently Robinson and co-workers duplicated this phenomenon in infants with primary tuberculosis.

Kveim Skin Test

This test was originally introduced by Williams and Nickerson in 1935, on the hypothesis that sarcoidosis might be a virus disease. Although a red papule was observed in four patients with suspected sarcoidosis and none in the controls, the nature of the skin reaction was not studied histologically, and the real significance of the test escaped recognition. Six years later Kveim discovered that the skin lesions duplicated histologically those of sarcoidosis. Shortly thereafter the Kveim test became widely accepted as a diagnostic test of sarcoidosis.

The Kveim test consists of an intradermal injection of saline suspension of sarcoid tissue, obtained from a patient with proved, active sarcoidosis. The development of a reddish nodule at the site of injection within approximately two months, which on histological examination reveals characteristic sarcoid structures, is indicative of sarcoidosis in the majority of suspects (Figure 88, cf. Figure 39). The site of inoculation has to be observed for at least six months before the test is considered negative. Positive skin tests have been obtained several years after inoculation.

The matter of "specificity" of the Kveim test is still not entirely settled. Sones and co-workers tested twenty-four patients with sarcoidosis and obtained sarcoidal Kveim reactions in 26.8 per cent of eighty-two tests. In nineteen patients with tuberculosis positive reactions were obtained in sixteen tests. In eighteen control subjects, 14.3 per cent of twenty-eight tests showed a positive sarcoidal reaction. The test was considered positive only if there was an epithelioid cell tubercle eight weeks after the intradermal injection. Clinically positive, but histologically nonspecific tests, revealed either nonspecific granulomatous tissue or chronic, nonspecific inflammation. Sones and his co-workers conclude that the clinical use of the Kveim test as an aid in the diagnosis of sarcoidosis is not justified. These conclusions are at variance with those of the majority of investigators.

The Kveim test is nonspecific since similar, although usually not identical tuberculoid skin responses have been obtained after injections with BCG vaccine, dead as well as virulent tubercle bacilli, normal spleen suspension, leukemic lymph node suspension and foreign bodies (beryllium, silica). However, the elicitation of a positive Kveim test confirms the presence of active sarcoidosis. In most cases, however, the disease can be diagnosed without the long wait necessary for a confirmatory Kveim test. In patients with regressing disease, the group in which one is usually in the greatest need of laboratory aid, the Kveim test is often negative. It should be noted that the administration of steroids interferes with the development of the sarcoid nodule.

Skin Tests in Fungous Diseases

As diseases caused by bacteria are being brought under control, fungous infections are assuming increasing importance, not only with respect to incidence but also with respect to

virulence The more frequent fungous infections which may affect the lungs and cause disseminated lesions of the type encountered in systemic diseases are histoplasmosis, coccidioidomycosis, moniliasis and the blastomycoses Although the presence of a mycotic infection may be suspected from the place of residence, symptoms and chest x-rays, a definitive diagnosis can seldom be made without confirmatory laboratory findings These involve the isolation of the fungus, complement fixation and skin tests

Skin tests are applied in the diagnosis of histoplasmosis, coccidioidomycosis and the blastomycoses The tests are administered and read in a manner similar to that of the tuberculin test Smith draws attention to the fact that skin tests in fungous diseases are negative in the initial stages of the infection and often even in advancing disease In fact, patients may progress to death without the development of positive skin tests This applies especially to histoplasmosis Terminal cases of histoplasmosis, coccidioidomycosis and blastomycosis frequently become anergic and give negative skin reactions A positive skin test in a fungous disease, like the tuberculin test, simply means present or past infection

Because of the occurrence of a common antigen in coccidioides immitis, Histoplasma capsulatum and Blastomyces dermatides skin tests may give cross-reactions For this reason, Smith advocates the simultaneous use of histoplasmin, coccidioidin and blastomycin, irrespective of whether or not a particular mycosis is suspected The specific reaction is always larger when the three antigens are given simultaneously and no difficulty is encountered in interpretation It should be mentioned that complement fixation tests for coccidioidomycoses, histoplasmosis and blastomycoses are of greater diagnostic value than skin tests This is due to the fact that antibodies are not simulated by subclinical infections and the titer continues to rise with advancing disease The problem of the isolation of fungi has been referred to earlier in the chapter

Chest Aspiration

Serous membrane involvement is a prominent feature of systemic diseases caused by lymphohematogenous infections, hypersensitivity states and metastatic neoplasms This book contains reference to serosal lesions of the pleura, pericardium, peritoneum and joints, especially to pleural effusions occurring in the course of the conditions mentioned Occasionally the appearance of a pleurisy heralds the onset or recrudescence of a systemic disease, although symptoms of the latter may not become apparent until months or years later In some cases the pleurisy is an abortive manifestation of what would ordinarily be a systemic disturbance

The classical example of the significance of an "idiopathic" pleural effusion is exemplified in tuberculosis Kallner examined 580 instances of "idiopathic" exudative pleurisy, one to twenty years later He found that no less than 39 per cent developed manifest tuberculosis Others have come to similar conclusions The prognostic implications of "idiopathic" pleurisies should not be lost sight of with respect to other diseases, notably the rheumatoid diseases, disseminated lupus erythematosus, diseases associated with other hypersensitivity states, malignant lymphomas and various other conditions described in previous chapters

A diagnostic chest aspiration is indicated in practically every patient found to have a pleural effusion even if the cause appears to be obvious The examination of the fluid does not necessarily lead to a correct diagnosis As a rule, an effusion in the young points to tuberculosis, in the elderly, to neoplasm A diagnosis of tuberculosis is established if acid fast organisms are cultured from the fluid The testing should be done before antituberculosis treatment is instituted The diagnosis of neoplasm may be established by the cytological examination of the fluid In spite of careful laboratory studies, a large proportion of pleural effusions cannot be diagnosed As indicated, some of these represent pleural manifestations of systemic diseases which may or may not be clinically apparent

The significance of fluid in the pleural space was studied by Tinney and Olsen In no less than 170 of 444 cases (38 per cent) a diagnosis

of the underlying disease was not established Of the 170 undiagnosed a tentative diagnosis of tuberculosis was made in fifty eight and of metastatic carcinoma in forty six In the remaining sixty six even less definite diagnoses were entertained The causes of pleural fluids exclusive of tuberculosis and carcinoma include congestive heart failure lymphoblastoma pneumonia cirrhosis of the liver chronic nephritis and nephrosis benign neoplasms of the ovary fungous diseases disseminated lupus erythematosus pulmonary infarction trauma to the thorax and subdiaphragmatic abscess

In differentiating transudates from exudates chief reliance is placed on the protein content the specific gravity of the fluid and to a lesser extent the presence of formed elements Paddock found a linear relationship between the protein content and the specific gravity which was as close as that in the blood In exudates the protein is generally more than 3 gm per cent and the specific gravity more than 1 020 The protein content is usually proportional to the degree of inflammation present It should be noted that bloody effusions although occurring more often in patients with malignant neoplasm are not diagnostic of cancer A high percentage of lymphocytes and a reduction of glucose (less than 60 mg per cent) are strongly indicative of tuberculosis

Bronchoscopy

Bronchoscopy is often employed in the diagnosis of obscure bronchopulmonary diseases including disseminated lesions of the type described in these pages Even if the cause seems obvious bronchoscopy may be indicated to rule out complicating elements or coexisting disease Bronchiogenic carcinoma is being encountered with increasing frequency in elderly males with pulmonary tuberculosis The latter is occasionally superimposed on sarcoidosis disseminated lupus erythematosus and malignant lymphomas As mentioned earlier in the chapter the bronchoscopic examination includes the obtainment of biopsy specimens and washings for exfoliative cytology bacteria fungi and foreign particles

In the diagnosis of disseminated pulmonary lesions commonly occurring in the course of systemic diseases bronchoscopy is done primarily to rule out carcinoma and tuberculosis the two conditions which often mimic the former It would seem however that insufficient use is made of bronchoscopy in its own right as an aid in the diagnosis of systemic diseases with pulmonary lesions Systemic diseases associated with tracheobronchial lymph node enlargement and there are quite a number of these may show changes in the mucosa and submucosa of adjacent bronchi Biopsies obtained from the latter may reveal important clues of the identity of the underlying disease In sarcoidosis for example the trachea and bronchi are occasionally involved and in several cases reported by Benedict and Castleman also Olsen it was possible to make a diagnosis by bronchoscopic biopsy In so called primary amyloidosis of the lungs the favorite sites of deposition of amyloid are in the trachea and major bronchi (see Chapter 3) Possibly hyperergic states and diffuse vascular diseases may also be reflected in changes in the bronchi A searching investigation along the lines indicated might prove fruitful

Needle Biopsy of the Liver

In the diagnosis of disseminated pulmonary lesions occurring in the course of systemic diseases a needle biopsy of the liver is occasionally helpful The test was originally introduced as a means of studying hepatic disease but it soon became apparent that tissues obtained by needle puncture of the liver may not only reveal intrinsic disease but also lesions associated with systemic disturbances

In a study of 650 needle biopsies of the liver Klatskin and Yesner found granulomatous lesions in patients with sarcoidosis tuberculosis erythema nodosum brucellosis viral infections including infectious mononucleosis and in actino



Figure 89 Needle liver biopsies A Small polygonal cells with poorly defined outlines and finely vesicular eosinophilic cytoplasm nuclei are ovoid hyperchromatic and exhibit occasional mitotic figures (Metastatic anaplastic carcinoma of liver primary in breast) B Small closely packed granuloma made up of epithelioid cells containing giant cells no caseation surrounding zone of thin fibrous bands separating granuloma from liver parenchyma (Sarcoidosis with hepatosplenomegaly)

mycosis These investigators refer to the reported occurrence of miliary hepatic granulomas in early syphilis leprosy, tularemia, coccidioidomycosis and blastomycosis To these may be added primary and metastatic carcinoma of the liver (Figure 89A), amyloidosis and leukemia The test is applicable to a wide variety of diseases

With respect to systemic diseases, probably the greatest field of application of needle liver biopsy *is in sarcoidosis (Figure 89B) This is not* surprising in view of the frequency of liver involvement in this disease In 1944, Pinner and I reviewed the published reports of forty-three autopsies on patients with sarcoidosis In no less than seventeen cases lesions were found in the liver Careful studies of the liver would have undoubtedly revealed a much higher incidence of hepatic involvement In twenty cases of histologically proved sarcoidosis Klatskin and Yesner were able to demonstrate submiliary granulomas by needle biopsy of the liver in fifteen but in none of the five with a presumptive diagnosis In ten of the former, the histological confirmation of the diagnosis rested on the liver biopsy findings alone Noteworthy was the finding of a striking resemblance in morphology between the hepatic lesions of sarcoidosis and those of tuberculosis erythema nodosum and brucellosis

Details of technique and the complications of needle biopsy of the liver do not concern us here Some investigators prefer the transthoracic approach in the ninth or tenth intercostal space in mid or anterior axillary line, others, the abdominal route The major complication is hemorrhage, especially if the needling is done in a jaundiced patient It is essential to administer vitamin K to the latter several days before the puncture is done and to have compatible blood

immediately available if needed Most physicians prefer not to do liver biopsy in such cases unless the latter is absolutely indicated

The incidence of complications following needling of the liver varies in the hands of different investigators In a collected series of 1200 liver biopsies, Sherlock found reports of eight deaths Among the 650 biopsy patients, reported by Klatskin and Yesner, there were a few minor but no fatal complications In a report by Morey and co-workers, on 139 needle biopsies of the liver, hemorrhage was encountered in four patients, in one of whom it proved fatal These authors noted that the incidence of hemorrhage and pain is much less when the puncture is made through the abdomen as compared to the transthoracic route



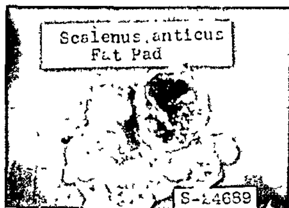




Figure 90 Prescalene lymph node biopsy A Hilar and right paratracheal lymph node enlargement, irregular, linear strands in subapical regions B Fat pad with lymph nodes removed from right prescalene space C Lymph node showing noncaseating sarcoid tubercles

Prescalene Lymph Node Biopsy

Systemic diseases associated with disseminated pulmonary lesions are often associated with lymph node enlargement. If a peripheral lymph node is available for biopsy, the histological changes are often decisive in the diagnosis. There are many occasions, however, when easily removable lymph nodes are not found and under these circumstances increasing use is being made of prescalene lymph node biopsy, a diagnostic procedure first proposed by Daniels in 1949. The method involves the removal of the lymph nodes or the lymphoid tissue from the fat filled space overlying the scalenus anticus muscle (Figure 90). Lymphatics of the right lung drain into the right paratracheal nodes; these drain also the inferior portion of the left lower lobe via the carinal nodes. Lymphatics of the upper mass of the left upper lobe drain into the left paratracheal nodes. But, lymphatics of the superior segment of the left lower lobe and those of the lingula drain into the left or right paratracheal nodes. For lesions of the left midlung, bilateral exploration is necessary (Connar).

The results obtained with prescalene lymph node biopsy depend on the nature of the material studied. In a representative group of 187 patients, reported by Shefts and co-workers, abnormal lymph nodes were found in sixty-seven (35.8 per cent). In suspected sarcoidosis the biopsy may give positive results in as high as 66 per cent (Cartensen and co-workers). In carcinoma, the incidence of finding metastatic invasion of the cervical lymph nodes is also quite high. In the presence of nondescript pulmonary disease such as unresolved pneumonia, unexplained hydrothorax or isolated pulmonary lesions, the prescalene lymph node biopsy is not often revealing. In forty-one such patients, Cuykendall found only eight showing specific lesions in the resected lymph nodes. In addition to sarcoidosis and metastatic malignancies, prescalene lymph node biopsy may give positive results in tuberculosis, malignant lymphomas, histoplasmosis, silicosis and several other conditions.

Harken and co-workers found that of seventy-eight proved cases of carcinoma of the lung thirty-one (40 per cent) showed metastases to the superior mediastinal or cervical lymph nodes. Harken's operation involves a cervicomediastinal exploration and the use of a laryngoscope as a lighted retractor in order to expose the upper mediastinal lymph nodes, a dissection much more extensive than that involved in Daniel's operation. One half of the positive results in Harken's cases came from tissues removed from the mediastinum and not the scalene fat pad. In an experience with 300 cervicomediastinal explorations Harken and co-workers encountered no serious complications. Hemorrhage occurred in two patients and pneumothorax in an additional two; the former was controlled with Gelfoam, the latter, with catheter drainage.

Lung Biopsy and Other Surgical Explorations

Scadding lists approximately eighty conditions which may be associated with diffuse nodular or reticular pulmonary lesions (Table 10). On the basis of chest x-rays, history, physical findings and the various laboratory tests described previously, it is possible to arrive at a correct diagnosis in possibly 50 per cent of cases. In the remainder a diagnosis cannot be made with any degree of certainty without the help of exploratory procedures, involving minor or major surgical operations. The most important of the latter is a lung biopsy. But even with the aid of a lung biopsy a diagnosis is not always possible for the reason that the appearance of the histological specimen may be in keeping with more than one condition.

A practical method of performing a lung biopsy with a minimum degree of danger to the patient, was first described by Klassen and co-workers, in 1949. With minor modifications, this procedure has been adopted and is being used with increasing frequency. The operation is done under general endotracheal anaesthesia since the latter facilitates inflation of the lung, when needed, and provides a patent airway at all times. A curved, lingular incision, approximately five

TABLE 10

List of Causes of Diffuse Nodular or Reticular Lung Shadows

Cause	Chronic	Acute
1 *Infections*		
Bacterial		
Tuberculosis		
miliary	+	+
acino-nodular	+	+
Streptococcal		+
Friedlander's bacillus		+
(Staphylococcal)		+
Brucellosis		+
Tularaemia		+
Mycotic		
Coccidioidomycosis	+	+
Histoplasmosis	+	+
Blastomycosis	+	+
Torulosis	?	+
Actinomycosis		+
Others		
Viral		
Unidentified pneumonotropic viruses		+
Varicella		+
Stevens Johnson syndrome		+
(Psittacosis)		+
Parasitic		
Schistosomiasis	+	
2 *Inhalation*		
Dusts		
Coal-miner's pneumoconiosis	+	
Silica	+	
Asbestos	+	
Beryllium	+	+
Aluminium	?	
Graphite	?	
Talc	?	
China clay	?	
Iron	+	
Barium	+	
Silver	+	
Manganese		+
Platinum osmium vanadium		+
Bagasse	+	+
Cotton		+
Mouldy hay grain etc		+
Irritant gases and vapours		
Phosgene		+
Nitrous fumes	+	+
Mustard gas, Lewisite		+
Others		
3 *Aspiration*		
Dysphagia pneumonitis	+	+
After coma		+
After resuscitation from drowning		+
After haemoptysis		+
Other forms of diffuse focal aspiration pneumonia		+
Kerosene		+
Liquid paraffin (lipoid pneumonia)	+	
Iodized oil	+	
4 *Associated with Cardiovascular Disease*		
Pulmonary oedema		+
Uraemic lung		+
(Rheumatic pneumonia)		
In mitral stenosis haemosiderosis	+	
miliary		
ossification	+	
Multiple pulmonary embolism	?	+
Right sided infective endocarditis	+	
5 *Of Uncertain Aetiology*		
Sarcoidosis		
Associated with erythema nodosum		
Diffuse interstitial fibrosis acute		
chronic		
Idiopathic pulmonary haemosiderosis		
6 *Associated with General Constitutional Diseases*		
Honeycomb lungs		
Developmental type		
Xanthomatosis		
Associated with biliary cirrhosis		
Associated with pituitary disorders		
Granuloma of unknown aetiology		
Mesodermal dysplasia (tuberous sclerosis)		
Rheumatoid arthritis		
Scleroderma		
Generalized lupus erythematosus		
Cystic disease of the pancreas		
7 *Reticuloses and Blood Diseases*		
Leukaemia		
Hodgkin's disease		
Mycosis fungoides		
Lymphosarcoma		
8 *Neoplastic*		
Primary bronchial carcinoma		
Metastatic blood borne		
lymphangitis carcinomatosa		
9 *Allergic*		
Eosinophilic infiltrations of the lungs		
Periarteritis nodosa		
Transient infiltrations in asthma		
10 *Associated with Bronchitis, Emphysema and Bronchiectasis*		
Diffuse fibrosis		
Cylindrical bronchiectasis		

(From Scadding *Tubercle*, 33 353 1952)

to six inches in length, is made over the fourth or fifth intercostal space below the breast The intercostal space selected depends upon the habitus of the individual The side showing the maximum pathology is chosen The incision is carried down through the subcutaneous tissues, pectoral and intercostal muscles To facilitate closure, a row of sutures is placed through the intercostal muscles along the upper and lower borders of the interspace selected before the pleural cavity is entered, permitting rapid closure and approximation of the ribs

After the pleural cavity is entered, the pleura is inspected and the lung palpated Immediately prior to incision of the pleura the anaesthetist is alerted and positive pressure applied and maintained until the muscles are closed In this way the lung is maintained in an inflated state during

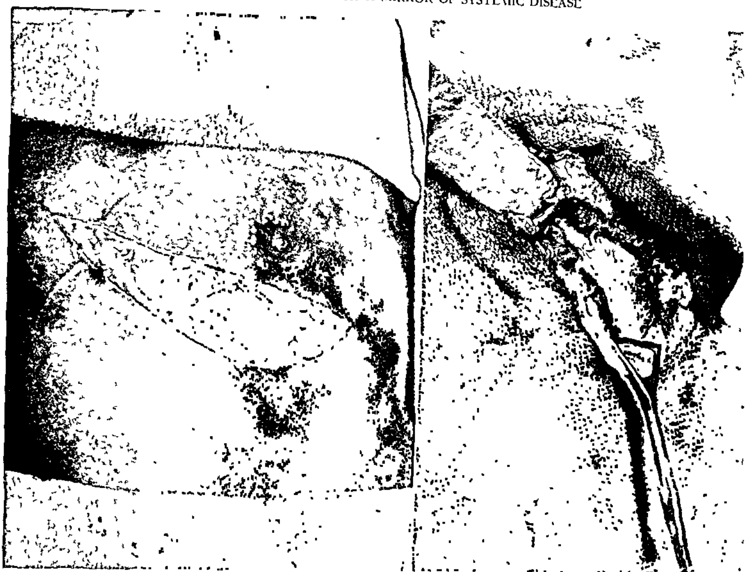


Figure 91 Lung biopsy A Inframammary intercostal incision B Edge of lung clamped and delivered through incision

the entire procedure thereby minimizing the risk of a large pneumothorax Depending on the side operated on, the anterior edge of the lower lobe or of the middle lobe on the right side, or of the lingula on the left, is grasped with a lung clamp and delivered through the incision (Figure 91) As a rule, it is not necessary to insert a retractor The lung segment is doubly clamped and the segment of the lung excised The raw edge is approximated with a continuous catgut suture proximally and interrupted sutures along the edge. After inspection for bleeding and air-leaks, the lung is permitted to retract into the pleural cavity and the chest wall is then resutured It is usually not necessary to apply waterseal drainage after the operation but a chest x-ray should be obtained soon after to determine the amount of pneumothorax, if any The procedure is well tolerated by patients even with low respiratory reserve

Table 11 lists the various diagnoses arrived at by three groups of investigators, in a collected series of 197 patients, after the performance of lung biopsies Approximately one-third of the patients were found to have diffuse, interstitial or idiopathic penumonitis with or without fibro-

TABLE 11

DIAGNOSIS OF PULMONARY LESIONS ESTABLISHED BY LUNG BIOPSY IN 197 PATIENTS

Categories	No of Cases	
1 Infections		21
A Tuberculosis	14	
B Fungous	6	
C Bronchitis	1	
2 Neoplasms		33
A Primary	5	
B Metastatic	28	
3 Inhalational Diseases		29
A Beryllhosis	10	
B Anthracosis or Silicosis or Combined	15	
C Asbestosis	4	
4 Sarcoidosis		33
5 Interstitial or Idiopathic Pneumonitis with or without Fibrosis and/or Emphysema		61
6 Miscellaneous (Eosinophilosis in association with diseases of hypersensitivity fibrocystic disease of pancreas lipidosis, vascular and nonspecific causes)		20
Total		197

(Combined results of Effler and co-workers Theodos and co-workers and Prior and co-workers [see Bibliography])

sis and/or emphysema (Figure 92) As indicated in Chapter 6, there is every reason to believe that continued use of lung biopsies will in time permit the differentiation of a number of agents which may cause diffuse interstitial lesions in the lungs It stands to reason that excised lung specimens, studied during the early dynamic phases of a disease, are invaluable in diagnosis The performance of a relatively simple operation, associated with a low morbidity, more than compensates for the greater danger involved in attempting to treat undiagnosed disease

As shown in Table 11, infections and neoplasms constitute sizable segments of the final diagnoses obtained in lung biopsies Inhalational diseases also constitute a large group If one combines the groups revealing sarcoidosis metastatic neoplasms variable numbers of diffuse interstitial fibroses and the miscellaneous it is apparent that more than 50 per cent of patients in whom lung biopsies are presently being performed reveal pulmonary lesions which are part of systemic disturbances

In order to obtain the maximum information from a lung biopsy, the histological examination of the resected specimen should be supplemented with as many additional examinations as possible Theodos and co workers stress the importance of utilizing microincineration and spectrophotometry in suspected inhalational disease Such examinations are of considerable value in forensic medicine Bacteriological and biochemical examinations of lung biopsy specimens, especially the latter, will in the future undoubtedly add greatly to our understanding of many currently obscure diseases

When a major lesion is present in the pleura, in a location where it can be readily approached by operation a pleural biopsy may be indicated In most instances one is dealing with an inflammatory, granulomatous or neoplastic disease which has provoked a thickly organized pleural membrane and it is difficult to ascertain the nature of the underlying disease The operation involves the resection of a portion of rib usually the eighth rib posteriorly, and the excision of small portions of the pleura In a series of twenty one pleural biopsies, Sutliff and co workers found the etiology of the pleurisy by means of pleural biopsy to be tuberculous in seventeen, carcinoma in three and N American Blastomycosis in one

Before concluding the section on operative procedures utilized in the diagnosis of disseminated pulmonary lesions mention should be made of aspiration needle biopsy and exploratory thoracotomy In the former operative complications, although in most instances of minor severity, are occasionally serious In addition, there is the danger of implanting disease in the chest wall by infection or tumor Moreover, the amount of needle aspirate obtained is often insufficient for diagnostic purposes For these reasons needle aspiration of the lung is rarely utilized excepting in instances of massive tumors, usually inoperable carcinomas, in which a definitive diagnosis has not been established Exploratory thoracotomy is a time consuming operation associated with considerable morbidity and its use is seldom warranted in the diagnosis of disseminated pulmonary lesions

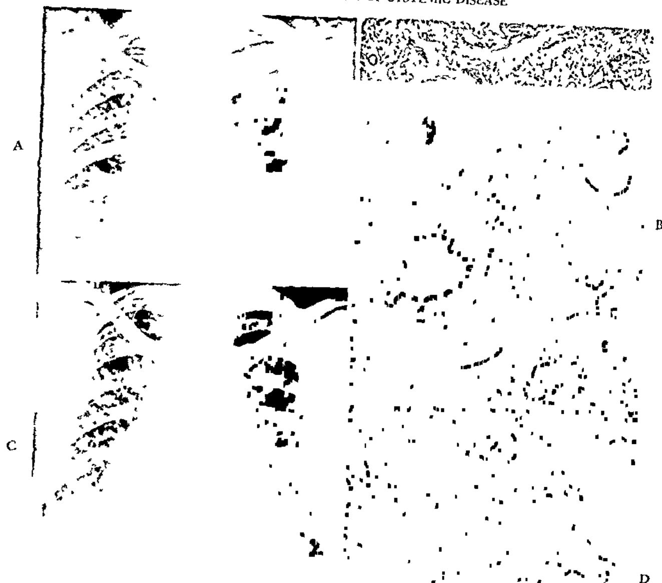


Figure 92 Lung biopsy A Li
meating both lung fields, incre
on right trachea and medias
right B Lung biopsy specime
acinar structures lined by hype
cells (Histologic features in k
tastatic malignancy) C Four
increase in interstitial striations
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By

ELI H RUBIN MD

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